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Patricia M Modrow   _8/31/99_

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13. ABSTRACT *(Maximum 200 words)*

The Autologous Blood and Marrow Transplant Registry (ABMTR) is a voluntary organization of 260 autotransplant centers that contribute clinical data on consecutive autotransplant recipients to a Statistical Center at the Medical College of Wisconsin. The ABMTR's database includes information for more than 16,500 women receiving autotransplants for breast cancer. According to data reported to the ABMTR, breast cancer is the most common indication for blood and marrow transplantation (allogeneic or autologous) in North America. This contract facilitated numerous enhancements to the ABMTR's clinical database, statistical support services and informational programs. These include collection of socioeconomic and clinical data on women receiving autotransplants for breast cancer and institutional data on centers doing transplants, streamlining data entry and management, development of appropriate statistical techniques for analyzing posttransplant data, and expansion of programs to provide access to collected data for patients, physicians and others involved in caring for women with breast cancer.

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_____ 11/30/98
PI - Signature   Date

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INTRODUCTION

Use of high-dose therapy with autologous blood or bone marrow hematopoietic support (autotransplants) to treat breast cancer continues to increase. According to data reported to the Autologous Blood and Marrow Transplant Registry (ABMTR), breast cancer was the most common indication for allogeneic or autologous blood or marrow transplantation in 1997-8. The ABMTR maintains a large database of clinical information on persons receiving autotransplants. This database provides important information relevant to breast cancer treatment. The purpose of the work funded in this contract was 1.) to enhance the existing ABMTR database so that important unresolved issues in use of autotransplants to treat breast cancer could be addressed and accurate information on autotransplants could be provided to women with breast cancer; and, 2.) to develop and make available appropriate biostatistical models for analyzing this database. Considerable progress was made during the four years of this contract including development of revised data collection forms, development of software for distributed data entry, computerization of log-in and error reporting processes, migration to state of the art computer hardware, completion of a survey of transplant center characteristics, evaluation of statistical models for analyzing transplant data, analysis of autotransplant results in persons with breast cancer, direct provision of data to patients and clinicians, presentation of data to national societies and organizations involved in planning breast cancer research, and implementation of a World Wide Web site with information related to autotransplants for breast cancer. Work began and continues (now without DAMD funding) in several other areas, including migration to a new database software system and implementation of a revised audit program. Accomplishments in each of the Technical Objectives outlined in our contract proposal is outlined below. Since this comprises the final report for DAMD17-95-1-5002, work in all four years is reviewed with focus on work in the fourth and final year.

PROGRESS IN ACHIEVING TECHNICAL OBJECTIVES

1.0 *Develop and enhance an observational database for autotransplants in breast cancer, including demographic, clinical, treatment, financial, and outcome data.*

1.1 Data collection

ABMTR centers are required to register all consecutive autotransplants with the ABMTR Statistical Center. Registration data include age, sex, race, disease stage and duration, graft type, graft treatment, conditioning regimen, graft treatment, and posttransplant disease status, survival and second cancers. Registration data allow analysis of trends in transplant use and outcome and identification of patients for specific studies. Comprehensive data are collected on a subset of these cases using the ABMTR Report Forms developed during Year 1 of this contract (Appendix 1). Report Forms were reviewed and underwent minor revisions in the fourth year of this contract, based on feedback from Statistical Center data management staff and participating centers. Data collection for 1994-1998 is summarized in Table 1.1.

Table 1.1 Accrual of autotransplants to the ABMTR database, 1994-1998.

Dates	Registration data		Report data	
	All diseases	Breast cancer	All diseases	Breast cancer
7/94 - 6/95	4,804	1,857	1,594	637
7/95 - 6/96	5,414	2,256	1,955	958
7/96 - 6/97	5,611	2,461	2,923	1,044
7/97 - 6/98	5,940	2,514	2,691	1,213
TOTAL	21,769	9,088	9,163	3,852

Two hundred sixty centers now participate in the ABMTR Research Program (Appendix 2). The ABMTR database now has registration data for a total of 16,723 recipients of autotransplants for breast cancer and comprehensive data for 5,479. The database is longitudinal; centers are requested to provide follow-up on survivors yearly.

As noted, data collection instruments (Report Forms) underwent major revisions during the first year of this contract (Appendix 1). Report Form enhancements included enhancements include collection of the following: 1.) income, occupation, educational level, and place of residence of autotransplant recipients; 2.) source and mode of payment for transplant procedure (insurer, fixed fee versus fee for service); 3.) inpatient versus outpatient setting for high-dose treatment; 4.) total number of hospital days in the first 100 days posttransplant; 5.) reason for using bone marrow versus peripheral blood stem cells for hematopoietic support; 6.) additional details regarding prior treatment for breast cancer; 7.) graft procurement procedures. In the final contract year, forms were reviewed and revised to improve clarity and collect additional data items, including *her2/neu* status of breast cancer tumors. Revisions are undergoing final review by Information Systems personnel who must program these changes into the database. Revised forms are expected to be in use by early 1999. The result of these enhancements and continued accrual of patients is a database with greater capabilities to address multiple issues relevant to breast cancer treatment. These data are increasingly used for timely clinical studies (see Section 4.0 below).

In the fourth contract year, Registration Forms were reviewed and are undergoing major revision so that more data can be collected on all patients and more sophisticated programs used to select patients for comprehensive reporting. A near final draft of the new Registration Form (Transplant Essential Data Form) is included in Appendix 1.

1.2 Uniform reporting of data

During the second year of this contract, work began on a revised Data Manual to accompany the new Report Forms. The revised Manual was distributed for review during the third contract year. Substantial modifications were requested by users. Work on a revised version was delayed by loss of personnel (Sandra Murphy, M.S., formerly the statistician for the Breast Cancer Working Committee, and Dr. Phil Rowlings) and subsequent training of new personnel. Work now continues under the supervision of Dr. Doug Rizzo and Diane Knutson with plans for distribution at the next IBMTR/ABMTR Participants' Meeting in March 1999.

Continuing the program of education for data managers in participating centers, the ABMTR conducted a two-day training session in January 1998, in conjunction with the ABMTR Annual Meeting in Keystone, Colorado (see Meeting Program and Evaluation Summary in Appendix 3). One hundred forty-two persons attended; 53 of these received travel grants to partially offset expenses of attending (see list of grantees in Appendix 3). This was the fourth data manager training session supported by DAMD funds. The DAMD travel grants, which were given preferentially to first time attendees, allowed many persons to attend who would not otherwise be able to participate. Participants indicated a high level of satisfaction with topics covered and training provided. In response to requests for additional sessions, a two-day training session was conducted by IBMTR/ABMTR Statistical Center personnel in November 1998 in Milwaukee (see Meeting Program and Evaluation Summary in Appendix 3). Forty-three data managers attended. Based on the positive feedback from participants, we now plan to hold two data manager training sessions per year to increase the opportunity for attendance. DAMD funding was critical in establishing this program of data manager training, both by allowing first-time attendance by data managers (many of whom now return annually) and by supporting personnel who have planned, conducted and refined the training program (specifically, D Knutson, A Kummerow, J Stone, L Lehrmann, B McGary, S Nell, J Rebro, D Rizzo, P Rowlings, SC Murphy).

1.3 Data review and entry

Forty of 260 ABMTR teams now submit Registration data on disk rather than paper. Statistical Center personnel continue to work on conversion programs to accommodate multiple data formats. Barbara Liu has primary responsibility for this task. During the second year of the contract, we computerized the log-in procedure for paper Report Forms to allow electronic comparison with data previously supplied on Registration. This provided verification of key fields; all discrepancies are resolved with the reporting center. During the third contract year, these programs were further developed and log-in procedures were streamlined. Thus, despite handling larger numbers of reports and verifying key fields, the lag time between Report Form receipt and log-in decreased from six to 1-2 months during this contract. Additionally, in the third and fourth year of the contract, we continued our work with StemCell Technologies to develop software for distributed data entry. Barbara McGary and Barbara Liu have primary responsibility for this collaboration. Patricia Vespalec and Ying Hu are involved in testing new StemSoft

programs. In December of 1997 a new version of BMTbase Registration was released which incorporated all new codes defined for our February 1998 registration period. This software, which includes the capability to generate disks for the ABMTR registration, was made available to all reporting centers free of charge and training in its use was provided at the Keystone meeting in January 1998. After working collaboratively with StemCell Technologies personnel to refine their programs, we recently received a copy of the soon to be released new version of BMTbase Reports for entering and submitting ABMTR Report Forms. The biggest advantage of this version over earlier versions is extensive data validation checking that occurs as data re entered at the reporting center. We worked with the software developers to include the data consistency checks normally done at the Statistical Center, particularly checking that event dates are reasonable chronologically. Catching incorrectly entered data at the time of entry by transplant center personnel, when it can be corrected quickly, means fewer errors to report back to the centers. Software (BMTransfer) to directly convert data entered on StemSoft software to a computerized format appropriate for incorporation in the IBMTR/ABMTR database was developed in cooperation with StemCell and was tested at the Statistical Center in the third and fourth contract years. This system is now operational. Sixty-five Centers are currently using the StemCell BMTbase Reports to enter report forms at their site and submit them to the registry. Twenty of these teams routinely submit these reports on disk; the remaining 45 are expected to do so within the next year.

During the fourth contract year, a computer program was developed by Barbara Liu to detect omissions, inconsistencies and out of range values as Report Forms are entered in the database at the Statistical Center and to automatically generate an error report to centers. Previously, the error report was generated manually by data entry personnel (Sharon Nell and Jane Rebro). The new system greatly increases the efficiency of this process and allows missing data to be provided and ambiguous data to be clarified quickly so that the database is as complete and accurate as possible. Centers are not reimbursed for their Report Forms until they respond to the error report providing an incentive for prompt resolution of problems.

1.4 Data validation

An Audit Schema was developed and approved in 1995. Audits revealed a high level of accuracy for reported data and no evidence of selective reporting but there was dissatisfaction with the audit procedures expressed by auditors, audited centers and Statistical Center personnel. These included appropriate selection of auditors to avoid conflicts of interest, adequate instruction of auditors, adequate instruction for audited centers to prepare for audits, selection and numbers of reports and data fields audited, and format and timeliness of audit reports. Audit procedures were extensively reviewed at the 1997 Annual Meeting. Guidelines for auditors and for evaluation of audit reports were developed in the third contract year. Computer programs to select teams and cases for auditing were revised in the fourth contract year. Sessions on the audit program were included in the 1997 and 1998 Data Manager Education sessions. An Audit Coordinator was hired and trained in the fourth contract year (no DOD funds used). The new audit program is now being implemented with 50 centers scheduled for audit in the current

IBMTR/ABMTR fiscal year (7/98-6/99).

1.5 Computer capabilities

Our efforts to allow electronic data submission are outlined in Section 1.2 above. During the past two contract years, the inadequacy of Scientific Information Retrieval (SIR), which has been the Statistical Center's database platform since 1980, to meet the challenges of collecting and managing an ever increasing volume of data became increasingly apparent as we attempted to implement functionalities to improve the efficiency of data handling. SIR had not kept pace with developments in database technology over the past 3-5 years. Limitations included a character-based rather than graphical user interface, lack of screen painters or report painters, the requirement to develop screens and entry-time validation in a non-standard command language, no mechanism for defining multi-step transactions or automatic maintenance of relationships between tables, and no mechanism to access SIR databases directly from third party analysis or applications development software, preventing us from using powerful tools available from other vendors. Declining availability of technical support and software upgrades were additional problems. Consequently, a review of currently available database software was done during the third contract year to assess new platforms by B McGary, B Liu, JP Klein, MJ Zhang and MM Horowitz. An outline of needed functionalities was also done. This included a careful analysis of data flow patterns, reimbursement tracking and communications between the Statistical Center and participating transplant centers as well as extensive error and validity checking. A preliminary plan for conversion of the IBMTR/ABMTR database from the current SIR to Oracle was developed. Work on this project was begun in the third contract year and continued in the fourth contract year. A consultant was hired to assist in the evaluation of database platforms and applications development software, to work with our staff to define the system requirements and begin the programming work. The decision was made to store the research data in an ORACLE database on a UNIX file server. UNIX was selected for this purpose over a PC server because of the more robust security and maturity of the operating system functions for backup and other utilities and because of power & speed possible. PCs were chosen as the client machine for the data entry /maintenance/reporting application because of the familiarity of the Windows environment and true compatibility between various applications by using Windows standards. VisualBasic was selected as the programming tool for building the application on the PC for use by our data entry and administrative staff. Reports and data extracts produced by the VisualBasic application can be clipped and pasted to any word processing document or spread sheet. SAS was defined as the analysis tool for use by the statistical staff. The ORACLE database can be accessed directly through a utility provided by SAS from the statisticians UNIX workstation or PC. After a developing a detailed design document and database specification, programming began. IBMTR/ABMTR personnel worked with the consultant to assist with the development and to provide continuity for future maintenance after the consultant completed the implementation of the first phase, which was to program the underlying database structure for both the Registration and Research database and to move the Registration database to ORACLE. The initial plan was to use our existing HP UNIX machine to

house our ORACLE database, but their limitations and the expense of HP upgrading made us seek a better alternative. We subsequently purchased two much more powerful SUN UNIX fileservers as well as five SUN workstations for statistical analysis and modeling. The performance advantages of the new machines seemed to outweigh any delay involved by not being able to install ORACLE immediately. VisualBasic programming work continued on the PC platform using Microsoft ACCESS on the PC for the preliminary database for testing. Database communication with ACCESS was through ODBC, the same communication gateway that was to be used with ORACLE. The delay for the delivery of the new machines, the installation and configuration of the operating system and network took much longer than scheduled. We were not able to install ORACLE on the SUN server until September of this year. Phase I of this project includes an integrated PC application to register new transplants, log in Report Forms whether they come to us on paper or disk, and allow entry of update information requested twice a year. All incoming data is compared to existing data and discrepancies are logged for reporting to the transplant teams. Features of this system that go beyond our current capabilities include:

1. Maintenance of information about the reporting centers as part of the database for statistical analysis and administrative functions;
2. Logging modifications to data, maintaining a history of changes to the data with *when, why* and *by whom* information;
3. Allowing attachment of notes to any data item as well as a general note page for each patient to store pertinent information not covered directly by the questions on the forms;
4. Stored information about data that violate validation rules as part of the database. Error/missing data reports are generated from these error flags. Error flags are cleared when the reporting center provides a correction;
5. A dynamic code table allows additional codes for new treatments; diagnosis codes or outcome categories to be added easily without changes or recompilation of the application code.

Testing is now underway on all features of the Phase I project. B Liu, B McGary, F Loberiza, P Vespalec, J Stone, S Nell, J Rebro, P Vespalec and Y Hu are all involved in this project. Communication from the PC application to the ORACLE database has been established. Substantial amounts of data have been converted from the SIR databases and loaded to ORACLE. Problems that occur during the testing process are logged to a database, prioritized and tracked through resolution. The Phase II component of the IBMTR/ABMTR database system is also underway to carry the basic features of the Phase I project to the much more complex structure to house all the data elements contained in our comprehensive Report Forms and to provide statistical access to the ORACLE database from SAS. We have contracted with a new department at the medical college (The Informatics Resource Center) for assistance with this phase. They provide expertise with SAS/ORACLE communication as well as data warehousing strategies to provide the statisticians a view of the data that is consistent, where data is only available after meeting the required validation standards. The status of this component so far is that a replica of the 12 tables now holding the information collected on our CORE form,

the Report Form data that is common to all diseases and all types of grafts, has been constructed in ORACLE on the SUN system. A substantial sample of data from the current SIR research data has been extracted and loaded to the ORACLE replica. The link between SAS and the ORACLE database has been established.

These database enhancements, made possible through funds provided by the DAMD, the National Cancer Institute and the Medical College of Wisconsin, are a major advance in our ability to handle large volumes of data, use advanced statistical techniques and provide information to the medical and general community.

2.0 ***Identify institutional characteristics of centers performing autotransplants for breast cancer in the United States and Canada, including academic affiliation, patient volume, physician training, staff/patient ratio.***

The institutional survey designed in Year 1 was completed in Year 2. Analysis of responses was done in collaboration with the American Society for Blood and Marrow Transplantation which also conducted a survey of U.S. transplant centers focusing on monitoring high-dose chemotherapy administration (see reprint in Appendix 4). Additional analyses of these data have been incorporated into completed and ongoing studies of autotransplants in breast cancer (see Section 4.0).

3.0 ***Evaluate and develop statistical models and software for effectively analyzing transplant data.***

Statistical Center faculty, particularly Drs. JP Klein and Dr. MJ Zhang, often working in collaboration with other Medical College of Wisconsin (MCW) and non-MCW faculty as well as with Biostatistics graduate students, were successful in exploring diverse aspects of statistical analysis of transplantation data, with publication of novel approaches in peer-reviewed journals. They have also made these and other useful statistical approaches available by posting SAS macros on the World Wide Web. A summary of their work follows. Reprints of publications are included in Appendix 4.

3.1 Proportional hazards regression with random groups effects. Frailty models are used in survival analysis to model unobserved heterogeneity or to model group effects (e.g. center effects). The model for group effects assumes that, conditional on a random effect, individuals within a group follow a standard proportional hazards model multiplied by the random effect. Common models for the random effect are the gamma distribution, the inverse Gaussian distribution, and the positive stable model. SAS macros were developed to fit these three models. The macros are available at the Division of Biostatistics Website (www.biostat.mcw.edu).

3.2 Accelerated failure time models with random effects. To date, all models for random effects are based on a multiplicative model for the effect of frailty on the conditional hazard rate. Drs. John Klein and Mei-Jie Zhang at the ABMTR Statistical Center have studied an alternative model in which an accelerated failure time model is assumed, conditional on the frailty. The common frailty in a group either adds or subtracts a

common amount from each group member's log survival times. Assuming a Gaussian distribution for the frailty and for the log survival times, this leads to a multivariate normal model for the life lengths within a group. Maximum likelihood estimates of the model parameters are obtained for this model and the properties of the model are studied. A paper discussing this approach will appear in *Biometrics* (Appendix 4.1)

3.2 <u>Joint modeling of the number of transfusions and time to death</u>. Drs. Klein and Hee-Chang Park (Changwon National University, South Korea) have looked at models for the number of transfusions a patient receives after transplant. The models look at joint models for numbers of transfusions and death times. Weibull models are assumed for the event times and Poisson models are assumed for the counts. The counts and event times are assumed to be independent given random effects which affect either the event time and/or the counts. In a paper under review for *Biometrics*, a common random effect is assumed and maximum likelihood estimates of the model parameters is assumed. This model allows one to study the effects of covariates on the counts and event times, to estimate the expected number of transfusions a patient may have at a given time, and to study the effects of the number on transfusions on survival. Alternative models to the common random effects model have been studied. These include models where the random effects are different for the counts and the event time, but these random effects are themselves correlated. These models are important for studying hematopoietic recovery after high-dose therapy. (Appendix 4.2)

3.3 <u>Comparison of statistical tests for center effects</u>. Drs. Klein, Zhang and Per Andersen (University of Copenhagen) have completed a Monte Carlo study of methods for testing for the presence of a center effect following a Cox regression analysis. The study compared an approach which treats center effects as fixed versus an approach which treats center effects as random. Random effects were tested using a score test. The study found that the random effects test worked quite well for small to moderate samples when either the random effects or fixed effects model held true. For the fixed effects model, larger sample sizes were required. When the sample size was small (<10 per center), the fixed effects model falsely rejected the hypothesis of a center effect when there was an effect. This study has important implications for analysis of multi-center trials. The results are to appear in *Statistics in Medicine* (Appendix 4.3). A SAS macro to perform the random effects score test has been developed and is available on our Website.

3.4 <u>Models for excess and relative mortality</u>. Drs. Klein and Zhang have studied techniques for comparing the mortality rates of transplant patients with standard published mortality rates. As opposed to existing techniques, these models allow for the incorporation of risk factors for transplant. Two models are considered. The first is the model for relative mortality. In this model the arbitrary baseline hazard rate in the Cox model is replaced by the known population hazard rate. The second is a model for excess mortality. Here a modification of the additive hazards model is used. Both models allow for point and interval estimates of the time after transplant when a transplant recipient with a given set of risk factors has a mortality rate which has returned to that in the reference population. This is important in studying long-term survivors of cancer treatment. The model for relative mortality is to appear in *Statistics in Medicine.*

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(Appendix 4.4)

3.5 <u>Confidence regions for the times when two survival curves are different</u>. Drs. Klein and Zhang have developed procedures to determine a confidence region for the times at which two treatments are different. The regions are based on either an assumed proportional hazards analysis or on an additive hazards regression model. Both models allow for the adjustment of fixed covariates. This is important when comparing treatments with different time patterns of adverse events. A paper discussing these methods is to appear in the *Journal of Planning and Inference* (Appendix 4.5). A second paper in this area has developed confidence bands, based on a proportional hazards model, for the difference in two survival curves. For this problem, the large sample distribution of the estimated covariate adjusted survival difference is quite intractable, so a novel method of simulating the correct confidence band is presented. The paper discussing this approach is under review (Appendix 4.6)

3.6 <u>Multistate modeling in survival analysis</u>. Dr. Klein has studied techniques for modeling the recovery process after a transplant as a dynamic function of intermediate events occurring after transplantation. The model can be used to provide a prediction of a patients ultimate prognosis at any point in time given the patient's history up to that time. With Dr. Qain (Ohio State University) a number of semi-parametric models and analyses have been developed. This material has appeared in the *Proceedings of the ASA Conference*. With a Ph.D. student from the University of Wisconsin, Dr. Klein is examining modifications of these models which allow for the incorporation of random effects (Appendix 4.7).

3.7 <u>General statistical analysis</u>. Dr. Klein has authored a book chapter for the volume, *Clinical Bone Marrow and Stem Cell Transplantation: Reference Textbook* which surveys statistical procedures commonly used in transplantation. He has also written an article for the *Encyclopedia of Statistics* on "Survival Distributions and their Characteristics." Dr. Zhang has contributed two short articles to the *Encyclopedia of Biostatistics* on techniques for grouped survival data. Dr. Klein, with Prof. Richard Johnson of the University of Wisconsin has authored an article for the *Handbook of Biostatistics* on regression techniques for censored (survival) data. (See Appendix 4.8-4.10 for Technical Reports describing the subjected matter included in these textbook chapters)

4.0 ***Provide access to data and biostatistical support for clinical studies related to autotransplants in breast cancer.***

During the four years of this contract, the ABMTR Working Committee initiated several studies of the use and outcome of autotransplants for breast cancer. A summary of studies completed and in progress follows. Reprints are found in Appendix 4.

4.1 <u>Overview of autotransplants for breast cancer.</u> *(Study chair: K. Antman, Columbia University, New York City; Study statistician: S.C. Murphy, ABMTR)*. This study described the increasing use of high-dose chemotherapy with autologous hematopoietic

stem cell support to treat high-risk breast cancer and analyzed outcome in 5,886 women. It documented a decrease in 100-day mortality from 22% in 1989 to 5% in 1995 (p<0.0001). Three-year PFS and survival probabilities (95% confidence intervals) were 65 (59-71)% and 74 (68-80)%, respectively, for stage 2 disease, and 60 (53-67)% and 70 (63-77)% for stage 3 disease. In stage 4 breast cancer, three-year probabilities of PFS and survival were 7 (4-10)% and 16 (12-20)%, respectively, for women with no response to conventional dose chemotherapy; 13 (9-17)% and 29 (25-33)% for those with partial response; and 32 (27-37)% and 46 (42-50)% for those with complete response. This study was published in the *Journal of Clinical Oncology* (Appendix 4.11).

4.2 <u>Prognostic factors in autotransplants for metastatic breast cancer</u>. *(Study chairs: K. Antman, Columbia University, New York City, P Rowlings, ABMTR; Study statistician: S.C. Murphy, ABMTR).* We analyzed data for 1,188 consecutive women receiving autotransplants for metastatic breast cancer in North America. Transplants were performed in 63 institutions between 1989 and 1995. The 2-year probability of survival was 42 ± 3% and progression-free survival, 18 ± 2%. Multivariate analyses identify older age, Karnofsky performance score < 90%, absence of estrogen receptors, metastases developing <18 months after adjuvant therapy, resistance to chemotherapy pretransplant, and more than two sites of disease or liver or central nervous system involvement as predictors of poor outcome. There is no significant difference in outcome among the most frequently used conditioning regimens. A manuscript is in press in the *Journal of the American Medical Association* (Appendix 4.12).

4.3 <u>Comparison of autotransplants with conventional chemotherapy for metastatic breast cancer</u>. *(Study chairs: D. Berry, CALGB, Duke University; J.D. Rizzo, ABMTR; Study statistician: D. Berry, CALGB and W Perez, ABMTR Statistical Center).* To date only one small (n=90 women) randomized trial has compared outcome of conventional therapy with autotransplants for metastatic breast cancer. This showed a modest survival advantage for autotransplants in women with newly diagnosed metastatic breast cancer. The validity and generalizeability of this results has been questioned. We are using the data set described in 4.1 above to study this issue in a large group of women by comparing autotransplants with conventional therapy of women treated on protocols of the Cancer and Leukemia Group B (CALGB). Statistical techniques and the detailed patient-level data available for these patients were used to adjust for differences in patient- and disease-related characteristics between the cohorts. Results indicate that outcome of women having complete or partial response to conventional dose chemotherapy is similar whether subsequent treatment includes conventional or high-dose chemotherapy. An abstract describing these results has been submitted for presentation at the 1999 American Society of Clinical Oncology meetings (Appendix 4.13) and a manuscript is in preparation.

4.4 <u>Prognostic factors in autotransplants for Stage II/III Breast Cancer</u>. *(Study chair: E. Reed, University of Nebraska, Omaha; Study statistician: W Perez, ABMTR).* In 1990, only 15% of autotransplants for breast cancer were in women with Stage II/III disease; in 1995 45% were for early stage disease. The ABMTR is studying outcome of autotransplants for 689 women with Stage II/III breast cancer to determine outcome and

identify prognostic factors. Median age was 43 (range, 28-66) years. Median number of involved axillary nodes was 12 (range, 0-46). More than 90% of women received an anthracycline-based chemotherapy regimen prior to high-dose therapy. The most commonly used conditioning regimens were cyclophosphamide and thiotepa (CT, 40%) and CT plus carboplatin (20%). A preliminary analysis of this data set was presented at the meeting of the American Society for Clinical Oncology in May 1997, Denver. At that time the median follow-up of this cohort was <2 years. The follow-up has been updated; median follow-up is now three years. Three-year probability of survival is 72% (95% confidence interval, 67-76%). Univariate and multivariate analyses of these data are provided in Appendix 4.14.

4.5 <u>Autotransplants in men with breast cancer</u>. *(Study chair: P. McCarthy, Roswell Park Cancer Institute, Buffalo; Study statistician: JD Rizzo, ABMTR)*. Breast cancer is rare in men. Consequently, there are few data regarding results of autotransplant for men with breast cancer. We studied 13 men receiving autotransplants for breast cancer and reported to the Autologous Blood & Marrow Transplant Registry (ABMTR) by 10 centers. Six men had Stage 2 breast cancer, four had Stage 3, and three had metastatic breast cancer. There were no unexpected regimen-related toxicities. Of ten men receiving autotransplants as adjuvant therapy, three relapsed three, five and 50 months posttransplant and died 16, 19 and 67 months posttransplant. Seven of ten are disease-free with median follow-up of 23 months (range, 6-50 months). Of three men treated for metastatic breast cancer, one had progressive disease and two recurrent disease at six, seven and 16 months posttransplant. Results appear similar to those reported for women receiving autotransplants for breast cancer. A manuscript describing these results has been submitted for publication (Appendix 4.15).

4.6 <u>Assessment of variation in costs of autotransplants for breast cancer among institutions</u>. *(Study chair: C. Bennett, Northwestern University, Chicago; Study statistician: T. Waters, Northwestern University, Chicago and J Stone, ABMTR Statistical Center)*. Preliminary data on more than 800 patients transplanted in four centers were analyzed. These data suggest that costs of autotransplants for breast cancer are significantly less than costs for transplants for hematologic malignancies. these data were presented at the 1998 American Society of Hematology meetings (Appendix 4.16). A manuscript is in preparation.

4.7 <u>Determination of second cancer risk after autotransplants for breast cancer</u>. *(Study chairs: M.M. Horowitz and JD Rizzo, ABMTR Statistical Center; Study statisticians: R. Curtis, National Cancer Institute and J Stone, ABMTR Statistical Center)* Increased surveillance for second cancers was part of several efforts at supplemental data collection under this contract. Centers registering second cancers are now asked to supply diagnostic information on Supplemental New Malignancy Forms (Appendix 1). We have identified 19 second primary breast cancers and 50 cancers of other types (18 leukemia/myelodysplasias, 6 cancers of the female genital tract, 6 skin cancers, 4 lung cancers, 3 thyroid cancers and 13 other cancers) thus far. Comparison of second cancer risk in women receiving autotransplants for breast cancer versus an age-, sex- and race-matched general population is in progress.

All of these studies were enhanced by the improved data collection, entry and management funded by this contract and by the greater level of detail now available on transplant recipients. Awareness of the resources of data and statistical expertise available through the Statistical Center is steadily increasing as are proposals to use the database for clinical research. To clearly delineate the procedures for proposing and conducting studies, Statistical Center staff developed a Statistician's Manual for studies using Registry data and statistical personnel (Appendix 5). This document helps focus study proposals, ensure that data handling and analysis are of high quality and ensure that the expertise of Registry Working Committees (Appendix 2) is fully utilized. Excerpts from these documents are now also available on our Website (www.ibmtr.org).

5.0   *Disseminate information regarding autotransplants for breast cancer to patients, physicians and others involved in care of women with breast cancer.*

The ABMTR database is a unique resource of information regarding use and outcome of transplants, containing data not readily available in the medical literature. Summary statistics on the use and outcome of autotransplants for breast cancer were included in the November 1997 issue of the ABMTR Newsletter (Appendix 6), which is widely distributed to transplant and oncology centers. These data are also available on-line at the IBMTR/ABMTR homepage on the World Wide Web (address: www.ibmtr.org; Appendix 7). In the fourth contract year we completely redesigned our Website to provide users with better understanding of the IBMTR/ABMTR's mission and organization and with better access to IBMTR/ABMTR data. Dr. M Horowitz, J Eder, L Lehrmann, S Nell and M Nugent spent considerable effort on this project. Answers to frequently asked questions and instructions for requesting additional information or proposing specific studies are given. These is also a link to a site, developed during the third and fourth contract years, with information regarding transplants for specific diseases, including breast cancer (see below). Report Forms may now be downloaded from the Website, which is anticipated to save the Statistical Center money in printing and mailing costs. Plans were developed for collecting data electronically and for Working Committee "chat rooms" although these functionalities will not be implemented until 1999.

There were many presentations of ABMTR data related to use and/or outcome of autotransplants for breast cancer during the four years of this contract year. Those presented at national and international meetings are listed in Appendix 8). Materials were provided for many other local presentations. Appendix 8 includes hard copy of a typical set of slides provided for such presentations. Additionally, the ABMTR, through its Information Resource program (partially funded by this contract) provides information regarding use and outcome of autotransplants for breast cancer physicians, patients and health-related agencies or companies. About 350 such requests were answered in the fourth contract year. Data provided in response to these requests often included survival and other outcome data not readily available in the medical literature. The importance of this resource to patients is reflected in a letter recently received from Mr. Clarence Mayer, husband of a women with breast cancer, and included, with his permission in Appendix 9. Individuals may now request such information through our Website.

In addition to www.ibmtr.org, in collaboration with the National Marrow Donor Program and the American Society of Blood and Marrow Transplantation, the ABMTR developed a World Wide

Web site with comprehensive information on the role of transplantation in treating various cancers. The site includes general transplant information, disease-specific information, and an "Ask the Expert" page where users may post questions which are triaged to appropriate persons for response. A comprehensive review of the role of high-dose chemotherapy in treating breast cancer was among the first topics to be made available. The Website was opened to the public in December 1997 at the following address: http://www.bmtinfo.org. Hard copies of pages relevant to breast cancer are enclosed in Appendix 7. Information is provided at basic (the average lay person) and technical (general physician or sophisticated lay person) levels, with an extensive bibliography aimed at transplant physicians that will be updated periodically, and with links to other relevant Web sites providing information on transplantation and cancer.

CONCLUSIONS

We are grateful for the support provided by the DAMD which has facilitated numerous enhancements to the ABMTR database and Statistical Center. This support enabled us to elevate the quality of information available for scientific studies and for health care providers and consumers. It also allowed us to make this information more available through peer-reviewed papers, educational materials and the World Wide Web.

FINAL REPORT - DAMD17-95-1-5002

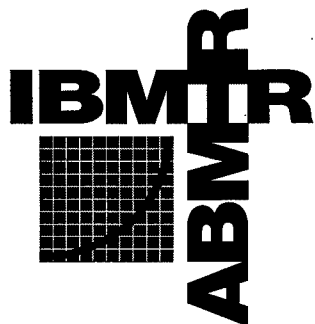Database of Autotransplants for Breast Cancer

Bibliography of all publications and meeting abstracts: see Appendix 4

<u>List of Personnel Receiving Pay from this Effort</u>
Bodine, Beverly A.
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Hogg, Susan J.
Horowitz, Mary M.
Hu, Ying
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Nell, Sharon
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IBMTR / ABMTR

APPENDICES

Grant No. DAMD17-95-1-5002

FINAL REPORT

"Database of Autotransplants for Breast Cancer"

Appendix 1	ABMTR Report Forms
Appendix 2	ABMTR Participating Centers and ABMTR Breast Cancer Working Committee
Appendix 3	1998 Data Management Sessions
Appendix 4	Publications/Analyses in progress
Appendix 5	Statisticians' Manual
Appendix 6	ABMTR Newsletters, including 1998 IBMTR/ABMTR Summary Slides
Appendix 7	World Wide Web Pages
Appendix 8	Presentations on Breast Cancer
Appendix 9	Letter of Support

Submitted to: U.S. Army Medical Research and Material Command

December 22, 1998

MEDICAL
COLLEGE
OF WISCONSIN

Statistical Center
Autologous Blood & Marrow Transplant Registry
Medical College of Wisconsin
8701 Watertown Plank Road • P.O. Box 26509
Milwaukee, WI 53226 USA

DAY 100 CORE FORM

TEAM ☐☐☐☐   IUBMID ☐☐☐☐☐☐
(Institutional Unique Blood or Marrow Transplant Identification Number)

Date of transplant for which this form is being completed: ☐☐ ☐☐ ☐☐
Month Day Year

Registry (circle one):   IBMTR   ABMTR

Date of report: ☐☐ ☐☐ ☐☐
Month Day Year
(Use same date on Graft Insert & Disease Insert for this transplant.)

Series 095
Reporting Forms

IBMTR / **ABMTR**

Statistical Center

Medical College of Wisconsin
P.O. Box 26509, 8701 Watertown Plank Road
Milwaukee, WI 53226
■ Telephone: 414-456-8325 ■ Fax: 414-456-6530

Day 100 post transplant: ☐☐ ☐☐ ☐☐
Month Day Year

Date of last actual contact with patient to determine medical status for this report: ☐☐ ☐☐ ☐☐
(See Q.6 on CORE Voucher for help determining date of last contact.)

—*(If patient died prior to Day 100 with no further infusions, enter date of death and check here ☐.)*

Demographics

* If this is a report of a second (or subsequent) transplant check here ☐, complete Disease Insert and go to Q.20

1. Institutional protocol number *(if applicable):* ☐☐☐☐☐☐☐☐☐☐☐

2. Was patient enrolled in cooperative group (eg. CALGB, CCG, EBMT, ECOG, EORTC, MRC, NAMTG, NSABP, POG, SWOG, etc.) study at any time or reported to the NMDP or EBMT? *(include transplant and non-transplant studies)*

   1 ☐ Yes
   0 ☐ No
   8 ☐ Unknown

Study 1:	**3.** Group_____	**4.** Study No._____	**5.** Patient No._____
Study 2:	**6.** Group_____	**7.** Study No._____	**8.** Patient No._____
Study 3:	**9.** Group_____	**10.** Study No._____	**11.** Patient No._____

12. Sex: 1 ☐ Male   2 ☐ Female

14. Date of birth: ☐☐ ☐☐ ☐☐
Month Day Year

13. Race: *(If patient's parents are from two separate groups of the following, check both)*

Caucasian/White
11 ☐ European or Western Russia
12 ☐ Middle East or North Coast of Africa
10 ☐ White, not otherwise specified

Black
21 ☐ African American
22 ☐ African Black (both parents born in Africa)
23 ☐ Caribbean Black
24 ☐ South or Central American Black
20 ☐ Black, not otherwise specified

Asian/Pacific Islander
31 ☐ Asian Indian
32 ☐ Filipino
33 ☐ Hawaiian (Polynesian)
34 ☐ Japanese
35 ☐ Korean
36 ☐ Northern Chinese
37 ☐ Southeast Asian/ Southern Chinese
30 ☐ Oriental, not otherwise specified

Hispanic
41 ☐ Caribbean Hispanic
42 ☐ Mexican or Southwestern USA Hispanic
43 ☐ South or Central American Hispanic
40 ☐ Hispanic, not otherwise specified

Native American
51 ☐ Native Alaskan/Eskimo/Aleut
52 ☐ American Indian
50 ☐ Native American, not otherwise specified

Other
90 ☐ Other, specify:_____
88 ☐ Unknown

Disease

15. What was the primary disease for which transplant was performed?
(Appropriate Insert must be submitted with this form)

10 ☐ Acute myelogenous leukemia (AML or ANLL)—

> 11 ☐ M1, myeloblastic
> 12 ☐ M2, myelocytic
> 13 ☐ M3, promyelocytic (APML, APL)
> 14 ☐ M4, myelomonocytic
> 15 ☐ M5, monocytic
> 16 ☐ M6, erythroblastic
> 17 ☐ M7, megakaryoblastic
> 18 ☐ Granulocytic sarcoma
> 19 ☐ Other, specify:_____
> 10 ☐ AML or ANLL unclassified
> *Complete Insert I and continue with Q.17 on Page 5*

20 ☐ Acute lymphoblastic leukemia (ALL)—

> 21 ☐ Mature B-cell (L3)
> 22 ☐ T-cell
> 23 ☐ Null cell (early Pre-B)
> 24 ☐ cALLa (includes Pre-B)
> 26 ☐ B-lineage
> 29 ☐ Other, specify:_____
> 20 ☐ ALL, unclassified
> *Complete Insert II and continue with Q.17 on Page 5*

40 ☐ Chronic myelogenous leukemia (CML)—

> 41 ☐ Ph¹ +; BCR/ABL+
> 42 ☐ Ph¹ +; BCR/ABL –
> 43 ☐ Ph¹ +; BCR/ABL unknown
> 44 ☐ Ph¹ –; BCR/ABL +
> 45 ☐ Ph¹ –; BCR/ABL –
> 46 ☐ Ph¹ –; BCR/ABL unknown
> 47 ☐ Ph¹ unknown; BCR/ABL +
> 48 ☐ Ph¹ unknown; BCR/ABL
> 49 ☐ Other, specify:_____
> 40 ☐ Ph¹ unknown; BCR/ABL unknown
> *Complete Insert III and continue with Q.17 on Page 5*

170 ☐ Multiple myeloma/Plasma cell disorder—

> 171 ☐ Multiple myeloma
> *Complete Insert VII and continue with Q.17 on Page 5*
> 172 ☐ Plasma cell leukemia
> *Complete Insert VII and continue with Q.17 on Page 5*
> 173 ☐ Waldenstrom macroglobulinemia
> 174 ☐ Amyloidosis
> 175 ☐ Solitary plasmacytoma
> 179 ☐ Other, specify:_____
> 170 ☐ Plasma cell disorders, unclassified
> *Continue with Q.16 on Page 5*

30 ☐ Other leukemia—

> 34 ☐ Chronic lymphocytic leukemia (CLL)
> 35 ☐ Hairy cell leukemia
> 37 ☐ Prolymphocytic leukemia (PLL)
> *Complete Insert IV and continue with Q.17 on Page 5*
> 36 ☐ Juvenile CML (no evidence of Philadelphia chromosome or BCR/ABL)
> *Complete Insert V and continue with Q.17 on Page 5*
> 38 ☐ M0, stem cell
> 31 ☐ Acute undifferentiated leukemia
> 32 ☐ Biphenotypic, bilineage or hybrid leukemia
> 33 ☐ Acute mast cell leukemia
> 39 ☐ Other, specify:_____
> 30 ☐ Other leukemia, unclassified
> *Complete Insert I and continue with Q.17 on Page 5*

50 ☐ Myelodysplastic/myeloproliferative disorders (MDS)
(Please classify all preleukemias)
(If patient has transformed to AML, also complete Insert I and indicate AML as the primary disease)—

> 51 ☐ Refractory anemia (RA)
> 52 ☐ Refractory anemia with excess blasts (RAEB)
> 53 ☐ Refractory anemia with excess blasts in transformation (RAEBT)
> 54 ☐ Chronic myelomonocytic leukemia (CMML)
> 55 ☐ Acquired idiopathic sideroblastic anemia (RARS)
> 56 ☐ Paroxysmal nocturnal hemoglobinuria (PNH)
> 57 ☐ Polycythemia vera
> 58 ☐ Essential or primary thrombocythemia
> 59 ☐ Myelofibrosis with myeloid metaplasia
> 60 ☐ Other myelofibrosis or myelosclerosis
> 69 ☐ Other myelodysplasia or myeloproliferative disorder, specify:_____
> 50 ☐ MDS, unclassified
> *Complete Insert V and continue with Q.17 on Page 5*

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100 ☐ Non-Hodgkin lymphoma *(If low grade lymphoma—101, 121, 102, 103—transformed before conditioning, use code 128)——*

101 ☐ Small cell lymphocytic
121 ☐ Small lymphocytic plasmacytoid
    (Lymphoplasmacytoid lymphoma)
102 ☐ Follicular, predominantly small cleaved cell
    (Grade I follicle center lymphoma)
103 ☐ Follicular, mixed, small cleaved and large cell
    (Grade II follicle center lymphoma)
104 ☐ Follicular, predominantly large cell
    (Grade III follicle center lymphoma)
105 ☐ Diffuse, small cleaved cell
    (Follicle center lymphoma, diffuse)
106 ☐ Diffuse, mixed, small and large cell
107 ☐ Diffuse, large cell
108 ☐ Large cell, immunoblastic (B-cell only)
125 ☐ Primary mediastinal large B-cell lymphoma
109 ☐ Lymphoblastic (Precursor B-lymphoblastic
    lymphoma/leukemia)
127 ☐ Precursor T-lymphoblastic lymphoma/leukemia
110 ☐ Small noncleaved cell, unclassified
111 ☐ Small noncleaved cell, Burkitt
112 ☐ Small noncleaved cell, non-Burkitt
113 ☐ Mycosis fungoides/Sezary syndrome
114 ☐ Histiocytic
115 ☐ Mantle cell
116 ☐ Composite, specify:_____
117 ☐ Large cell anaplastic lymphoma, Ki1 positive
118 ☐ Primary CNS lymphoma
122 ☐ Mucosal Associated Lymphoid Tissue type
    (Extranodal marginal zone B-cell lymphoma)
123 ☐ Nodal marginal zone B-cell lymphoma
124 ☐ Splenic marginal zone B-cell lymphoma
126 ☐ Large granular lymphocytic leukemia
128 ☐ Transformed low grade lymphoma
131 ☐ Angioimmunoblastic T-cell lymphoma
132 ☐ Angiocentric lymphoma
133 ☐ Intestinal T-cell lymphoma
134 ☐ Adult T-cell lymphoma/leukemia
    (HTLV1 associated)
139 ☐ Other peripheral T-cell lymphoma, specify:
    _____
130 ☐ Peripheral T-cell lymphomas, unclassified
119 ☐ Other non-Hodgkin lymphoma, specify:
    _____
100 ☐ Non-Hodgkin lymphoma, unclassified
    (Complete Insert VI and continue with **Q.17 on Page 5**)

150 ☐ Hodgkin lymphoma——

151 ☐ Lymphocyte predominant
152 ☐ Nodular sclerosis
153 ☐ Mixed cellularity
154 ☐ Lymphocyte depleted
159 ☐ Other Hodgkin lymphoma, specify:_____
150 ☐ Hodgkin lymphoma, unclassified
    (Complete Insert VI and continue with **Q.17 on Page 5**)

200 ☐ Other malignancies——

250 ☐ Breast cancer
    (Complete Insert VIII and continue with **Q.17 on Page 5**)
201 ☐ Head & neck
202 ☐ Lung, small cell
203 ☐ Lung, non-small cell
239 ☐ Lung, other
204 ☐ Mediastinal neoplasm, specify:_____
205 ☐ GI tract
206 ☐ Pancreatic
207 ☐ Hepatobiliary
208 ☐ Kidney & urinary tract
209 ☐ Prostate   212 ☐ Cervical
210 ☐ Testicular   213 ☐ Uterine
225 ☐ Germ cell tumor   214 ☐ Ovarian (epithelial)
211 ☐ External genitalia 215 ☐ Vaginal
216 ☐ Sarcoma unspecified
217 ☐ Soft tissue sarcoma
218 ☐ Bone sarcoma (excluding Ewing sarcoma)
219 ☐ Melanoma
220 ☐ Central nervous system tumor
    (Complete Insert XVIII and continue with **Q.17 on Page 5**)
221 ☐ Wilm tumor
222 ☐ Neuroblastoma
    (Complete Insert XVII and continue with **Q.17 on Page 5**)
223 ☐ Retinoblastoma
224 ☐ Ewing sarcoma
226 ☐ Medulloblastoma
227 ☐ PNET
231 ☐ Thymoma
269 ☐ Other malignancy, specify:_____
200 ☐ Other malignancies, unclassified
    (Continue with **Q.16 on Page 5**)

300 ☐ Severe aplastic anemia——

301 ☐ Idiopathic
302 ☐ Secondary to hepatitis
303 ☐ Secondary to toxin/other drug
304 ☐ Amegakaryocytosis (not congenital)
305 ☐ Schwachmann-Diamond
306 ☐ Acquired Pure Red Cell Aplasia
309 ☐ Other SAA, specify:_____
    (Complete Insert IX and continue with **Q.17 on Page 5**)

310 ☐ Inherited abnormalities of erythrocyte differentiation or function *(If patient has developed leukemia, also complete Insert for appropriate leukemia diagnosis)——*

311 ☐ Fanconi anemia
    (Complete Insert X and continue with **Q.17 on Page 5**)
312 ☐ Diamond-Blackfan anemia (pure red cell aplasia)
319 ☐ Other, specify:_____
    (Complete Insert IX and continue with **Q.17 on Page 5**)
355 ☐ Sickle Thalassemia major
356 ☐ Sickle cell anemia
359 ☐ Other hemoglobinopathy, specify:_____
350 ☐ Thalassemia major & oth hemoglobinop., unclass.
310 ☐ Inherited abnorm. of erythrocyte diff, unclass.
    (Complete Insert XI and continue with **Q.17 on Page 5**)

400 ☐ SCID and other disorders of the immune system

- 401 ☐ ADA deficiency severe combined immunodeficiency (SCID)
- 402 ☐ Absence of T and B cells SCID
- 403 ☐ Absence of T, normal B cell SCID
- 404 ☐ Omenn syndrome
- 405 ☐ Reticular dysgenesis
- 406 ☐ Bare lymphocyte syndrome
- 419 ☐ SCID other, specify:_____
- 451 ☐ Ataxia telangiectasia
- 452 ☐ HIV infection
- 454 ☐ DiGeorge anomaly
- 455 ☐ Chronic granulomatous disease
- 456 ☐ Chediak-Higashi syndrome
  Complete Insert XIX and continue with Q.17 on Page 5
- 457 ☐ Common variable immunodeficiency
- 458 ☐ X-linked lymphoproliferative syndrome
- 459 ☐ Leukocyte adhesion deficiencies, incl. GP180, CD-18, LFA and WBC adhesion deficiencies
- 460 ☐ Kostmann agranulocytosis (congenital neutropenia)
- 461 ☐ Neutrophil actin deficiency
- 462 ☐ Cartilage-hair hypoplasia
- 464 ☐ CD40 ligand deficiency
- 470 ☐ Combined immunodeficiency disease (CID), unspecified
- 474 ☐ CID other, specify: _____
- 479 ☐ Other immunodeficiencies, specify: _____
  Complete Insert XII and continue with Q.17 on Page 5
- 453 ☐ Wiskott Aldrich syndrome
  Complete Insert XIII and continue with Q.17 on Page 5

500 ☐ Inherited abnormalities of platelets

- 501 ☐ Amegakaryocytosis/congenital thrombocytopenia
- 502 ☐ Glanzmann thrombasthenia
- 509 ☐ Other inherited abnorm. of platelets, specify:_____
- 500 ☐ Inherited abnorm. of plate. unclassified
  Continue with Q.16 on Page 5

600 ☐ Autoimmune diseases

- 601 ☐ Myasthenia gravis
- 602 ☐ Multiple sclerosis
- 603 ☐ Rheumatoid arthritis
- 604 ☐ Psoriatic arthritis/psoriasis
- 605 ☐ Systemic lupus erythematosis (SLE)
- 606 ☐ Polymyositis-dermatomyositis
- 607 ☐ Scleroderma
- 608 ☐ Sjoegren syndrome
- 609 ☐ Polyarteritis nodosa
- 610 ☐ Wegener granulomatosis
- 611 ☐ Other vasculitis, specify:_____
- 612 ☐ Inflammatory bowel disease
- 629 ☐ Other autoimmune disease, specify:_____
- 600 ☐ Autoimmune disease unclassified
  Continue with Q.16 on Page 5

520 ☐ Inherited disorders of metabolism

- 521 ☐ Osteopetrosis (malignant infantile osteopetrosis)
  Complete Insert XV and continue with Q.17 on Page 5
- 522 ☐ Lesch-Nyhan (HGPRT deficiency)
- 523 ☐ Neuronal ceroid lipofuscinosis (Batten disease)

Mucopolysaccharidosis
- 531 ☐ Hurler syndrome (IH)
- 532 ☐ Scheie syndrome (IS)
- 533 ☐ Hunter syndrome (II)
- 534 ☐ Sanfilippo (III)
- 535 ☐ Morquio (IV)
- 536 ☐ Maroteaux-Lamy (VI)
- 537 ☐ β-glucuronidase deficiency (VII)
- 538 ☐ Mucopolysaccharidosis (V)
- 539 ☐ Other mucopolysaccharidosis, specify:
  _____
- 530 ☐ Mucopolysaccharidosis, unclassified

Mucolipidoses
- 541 ☐ Gaucher disease
- 542 ☐ Metachromatic leukodystrophy (MLD)
- 543 ☐ Adrenoleukodystrophy (ALD)
- 544 ☐ Krabbe disease (globoid leukodystrophy)
- 545 ☐ Neimann-Pick disease
- 546 ☐ I-cell disease
- 547 ☐ Wolman disease
- 548 ☐ Glucose storage disease
- 549 ☐ Lysosomal storage disease
- 559 ☐ Other mucolipidoses, specify:
  _____
- 540 ☐ Mucolipidoses, unclassified

Polysaccharide hydrolase abnormalities
- 561 ☐ Aspartyl glucosaminuria
- 562 ☐ Fucosidosis
- 563 ☐ Mannosidosis
- 569 ☐ Other polysaccharide hydrolase abnorm., spec.:
  _____
- 560 ☐ Polysaccharide hydrolase abnorm., unclassified
- 529 ☐ Other inherited metabolic disorders, specify:
  _____
- 520 ☐ Inherital disorders of metabolism, unclassified
  Complete Insert XIV and continue with Q.17 on Page 5

570 ☐ Histiocytic disorders

- 571 ☐ Familial erythrophagocytic lymphohistiocytosis (FEL, Familial hemophagocytic lymphohistiocytosis)
- 572 ☐ Histiocytosis-X
- 573 ☐ Hemophagocytosis
- 574 ☐ Malignant histiocytosis
- 579 ☐ Other histocytic disorder, specify:
  _____
- 570 ☐ Histocytic disorder, unclassified
  Continue with Q.16 on Page 5

900 ☐ Other

- Specify: _____
  Continue with Q.16 on Page 5

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Clinical Status of Patient Prior to Conditioning

16. Date of diagnosis of primary disease: ☐☐☐☐☐☐   *Complete only if a disease-specific*
    Month   Day   Year   *Insert is not required.*

17. *Allografts only:* Patient's blood type:
    1 ☐ A Rh+   5 ☐ A Rh−   9 ☐ A Rh unknown
    2 ☐ B Rh+   6 ☐ B Rh−   10 ☐ B Rh unknown
    3 ☐ AB Rh+   7 ☐ AB Rh−   11 ☐ AB Rh unknown
    4 ☐ O Rh+   8 ☐ O Rh−   12 ☐ O Rh unknown
                                     88 ☐ Unknown

18. Has patient ever been pregnant?
    1 ☐ Yes ──── **19.** Number of pregnancies (Gravida): ☐☐
    0 ☐ No

    8 ☐ Unknown

    7 ☐ Not applicable (patient is male, or a female child)

20. Did patient receive blood transfusions at <u>any time prior to conditioning</u>?
    1 ☐ Yes ──── **21.** Give number (best estimate) of <u>donor exposures</u>:
    0 ☐ No   1 ☐ 1 - 5   5 ☐ 31 - 40
    8 ☐ Unknown   2 ☐ 6 - 10   6 ☐ 41 - 50
                      3 ☐ 11 - 20   7 ☐ > 50
                      4 ☐ 21 - 30   8 ☐ Unknown

22. What was the functional status of patient prior to conditioning?

> *If the patient is 16 years of age or older, complete the Karnofsky Scale.*
> *If patient is younger than 16 years of age, complete the Lansky Scale.*
> *Rate activity of patient immediately prior to initiation of conditioning.*

Karnofsky Scale (age ≥16 yrs)
Select the phrase in the Karnofsky Scale which
best describes the activity status of the patient:

Able to carry on normal activity; no special care is needed.
    100 ☐ Normal; no complaints; no evidence of disease
    90 ☐ Able to carry on normal activity
    80 ☐ Normal activity with effort

**Unable to work; able to live at home, care for most
personal needs; a varying amount of assistance is needed.**
    70 ☐ Cares for self; unable to carry on normal activity
        or to do active work
    60 ☐ Requires occasional assistance but is able to
        care for most needs
    50 ☐ Requires considerable assistance and frequent
        medical care

**Unable to care for self; requires equivalent of institutional
or hospital care; disease may be progressing rapidly.**
    40 ☐ Disabled; requires special care and assistance
    30 ☐ Severely disabled; hospitalization indicated,
        although death not imminent
    20 ☐ Very sick; hospitalization necessary
    10 ☐ Moribund; fatal process progressing rapidly

Lansky Scale (age <16 yrs)
Select the phrase in the Lansky Play-Performance Scale
which best describes the activity status of the patient:

Normal range.
    100 ☐ Fully active
    90 ☐ Minor restriction in physically strenuous play
    80 ☐ Restricted in strenuous play, tires more easily,
        otherwise active

Mild to moderate restriction.
    70 ☐ Both greater restrictions of, and less time spent
        in, active play
    60 ☐ Ambulatory up to 50% of time, limited active play
        with assistance/supervision
    50 ☐ Considerable assistance required for any active
        play; fully able to engage in quiet play

Moderate to severe restriction.
    40 ☐ Able to initiate quiet activities
    30 ☐ Needs considerable assistance for quiet activity
    20 ☐ Limited to very passive activity initiated by others
        (i.e., TV)
    10 ☐ Completely disabled, not even passive play

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23. Was there clinically significant coexisting disease or organ impairment prior to conditioning?
(Report liver disease in Q.63-69)

₁ ☐ Yes
₀ ☐ No

What were the diagnoses?

	Yes	No	
24.	₁☐	₀☐	Significant *hemorrhage* (e.g. CNS or GI), specify site(s): _____
			_____

Cardiovascular

25. ₁☐ ₀☐ Coronary artery disease
26. ₁☐ ₀☐ Hypertension
27. ₁☐ ₀☐ Other cardiac disease, specify: _____

Endocrine

28. ₁☐ ₀☐ Diabetes mellitus
29. ₁☐ ₀☐ Thyroid disease
20. ₁☐ ₀☐ Other endocrine disease, specify:_____

CNS

31. ₁☐ ₀☐ Seizure disorder
32. ₁☐ ₀☐ Other CNS disease, specify: _____

Pulmonary

33. ₁☐ ₀☐ Asthma
34. ₁☐ ₀☐ Other pulmonary disease, specify: _____

35. ₁☐ ₀☐ *Genitourinary* disease, specify: _____
36. ₁☐ ₀☐ *Gastrointestinal* disease, specify: _____
37. ₁☐ ₀☐ *Hematologic* disease, specify: _____

Chromosomal

38. ₁☐ ₀☐ Fanconi anemia
39. ₁☐ ₀☐ Down syndrome
40. ₁☐ ₀☐ Other chromosomal disorders, specify:_____

41. ₁☐ ₀☐ History of *other malignancy*, specify:_____
42. ₁☐ ₀☐ *Neonatal GVHD*

Autoimmune disease

43. ₁☐ ₀☐ Rheumatoid arthritis
44. ₁☐ ₀☐ Systemic lupus erythematosis
45. ₁☐ ₀☐ Multiple sclerosis
46. ₁☐ ₀☐ Polyarteritis nodosa
47. ₁☐ ₀☐ Psoriasis
48. ₁☐ ₀☐ Other autoimmune disease, specify:_____

49. ₁☐ ₀☐ *Other*, specify: _____

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Organ Function Values Just Prior to Conditioning

Liver function:

			Specify Units	Date tested: Month Day Year	Not Tested

AST (SGOT)

50. ☐☐☐.☐☐ ₁☐U/L ₂☐μkat/L 51. ☐☐☐☐☐☐ ☐

52. ☐☐☐.☐☐ Upper limit of normal

ALT (SGPT)

53. ☐☐☐.☐☐ ₁☐U/L ₂☐μkat/L 54. ☐☐☐☐☐☐ ☐

55. ☐☐☐.☐☐ Upper limit of normal

Total serum bilirubin

56. ☐☐☐.☐ ₁☐mg/dL ₂☐μmol/L 58. ☐☐☐☐☐☐ ☐

59. ☐☐☐.☐ Upper limit of normal

LDH

60. ☐☐☐☐☐.☐ ₁☐U/L ₂☐μkat/L 61. ☐☐☐☐☐☐ ☐

62. ☐☐☐☐☐.☐ Upper limit of normal

63. Did patient have known clinical liver disease (eg. viral hepatitis) at any time prior to conditioning?

₁☐ Yes——— Specify:

₀☐ No

	Yes	No	Unknown	
64.	₁☐	₀☐	₈☐	Hepatitis B
65.	₁☐	₀☐	₈☐	Hepatitis A
66.	₁☐	₀☐	₈☐	Hepatitis C
67.	₁☐	₀☐	₈☐	Drug toxicity
68.	₁☐	₀☐	₈☐	Other, specify: _____

69. Date of onset: ☐☐ ☐☐ ☐☐ ☐Date Unknown
Month Day Year

Serum creatinine just prior to conditioning:

		Specify Units	Date tested: Month Day Year	Not Tested

70. ☐☐☐.☐☐ ₁☐mg/dL ₂☐mmol/L ₃☐μmol/L 72. ☐☐☐☐☐☐ ☐

Hematologic Findings Just Prior to Conditioning

Date of CBC: ☐☐☐☐☐☐
Month Day Year

Actual CBC results

		Specify Units	Transfused	Not Tested
WBC:	☐☐☐☐☐☐.☐	₁☐ x10⁹/L ₂☐ x10⁶/L	☐	☐
Neutrophils:	☐☐ %		☐	☐
Lymphocytes:	☐☐ %		☐	☐
Hemoglobin:	☐☐☐.☐☐	₁☐ g/dL ₂☐ g/L ₃☐ mmol/L	☐	☐
Hematocrit:	☐☐ %		☐	☐
Platelets:	☐☐☐☐☐☐	₁☐ x10⁹/L ₂☐ x10⁶/L	☐	☐

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73. Patient smokes cigarettes, or has in the past:

1 ☐ Yes ────┐
0 ☐ No   │ **74.** Average number of packs per day: [ ].[ ]   8 ☐ Unknown
8 ☐ Unknown │ **75.** Number of years: [ ][ ]   8 ☐ Unknown

76. Was clinically important infection(s) present or being treated <u>within one week prior to conditioning</u>?
Note: Report later infections on page 30 of this report.

1 ☐ Yes ──┐
0 ☐ No   │ Select site and organism from lists shown on the next page and place number in the appropriate spaces. If more than one site or organism were involved, list one site of infection and organism on the first line, second site and/or organism on second line.

*If more than two infections of any category, check here ☐ and copy page
to provide information on 3rd or subsequent infection (do <u>not</u> report in Q.106-110).*

		Site		**Organism**

77. ☐ Bacterial

<u>Typical</u>   First   **78.** [ ][ ]   **79.** _____

Second   **80.** [ ][ ]   **81.** _____

<u>Atypical</u>   First   **83.** [ ][ ]   **84.** [B][ ][ ]

Second   **85.** [ ][ ]   **86.** [B][ ][ ]

87. Other atypical bacterium, specify: _____

88. ☐ Fungal   First   **89.** [ ][ ]   **90.** [F][ ][ ]

Second   **91.** [ ][ ]   **92.** [F][ ][ ]

93. Other fungus, specify: _____

94. ☐ Viral   First   **95.** [ ][ ]   **96.** [V][ ][ ]

Second   **97.** [ ][ ]   **98.** [V][ ][ ]

99. Other virus, specify: _____

100. ☐ Parasitic   First   **101.** [ ][ ]   **102.** [P][ ][ ]

Second   **103.** [ ][ ]   **104.** [P][ ][ ]

105. Other parasite, specify: _____

106. ☐ Other infections   First   **107.** [ ][ ]   **108.** [O][ ][ ]

Second   **109.** [ ][ ]   **110.** [O][ ][ ]

Codes for Common Sites of Infection

1 Blood/buffy coat	40 *Genito-Urinary Tract unspecified*
2 Disseminated – generalized, isolated at 3 or more distinct sites	41 Kidneys, renal pelvis, ureters and bladder
	42 Prostate
3 *Central Nervous System unspecified*	43 Testes
4 Brain	44 Fallopian tubes, uterus, cervix
5 Spinal cord	45 Vagina
6 Meninges and CSF	50 *Skin unspecified*
10 *Gastrointestinal Tract unspecified*	51 Genital area
11 Lips	52 Cellulitis
12 Tongue, oral cavity and oro-pharynx	53 Herpes Zoster
13 Esophagus	54 Rash, pustules or abscesses not typical of any of the above
14 Stomach	
15 Gallbladder and biliary tree (not hepatitis), pancreas	60 *Central venous catheter unspecified*
16 Small intestine	61 Catheter insertion or exit site
17 Large intestine	62 Catheter tip
18 Feces/stool	70 Eyes
19 Peritoneum	75 Ear
20 Liver	81 Joints
30 *Respiratory unspecified*	82 Bone marrow
31 Upper airway and nasopharynx	83 Bone cortex (osteomyelitis)
32 Laryngitis/larynx	84 Muscle (excluding cardiac)
33 Lower respiratory tract (lung)	85 Cardiac (endocardium, myocardium, pericardium)
34 Pleural cavity, pleural fluid	86 Lymph nodes
35 Sinuses	87 Spleen

Codes for Commonly Reported Organisms

1. Bacteria (Indicate code for atypical bacteria; list bacterium for non-atypical bacteria in Q.79, 81.)

100 Atypical bacteria, not otherwise specified
101 Coxiella
102 Legionella
103 Leptospira
104 Listeria
105 Mycoplasma
106 Nocardia
107 Rickettsia
110 Tuberculosis, NOS (AFB, acid fast bacillus, Koch bacillus)
111 Typical tuberculosis (TB, Tuberculosis)
112 Mycobacteria (avium, bovium, intracellulare)
113 Chlamydia
119 Other atypical bacteria, *specify in Q.87*

2. Fungal Infections
200 Candida, not otherwise specified
201 Candida albicans
202 Candida krusei
203 Candida parapsilosis
204 Candida tropicalis
205 Torulopsis glabrata (a subspecies of candida)
209 Other Candida, *specify in Q.93*
210 Aspergillus, not otherwise specified
211 Aspergillus flavus
212 Aspergillus fumigatus
213 Aspergillus niger
219 Other Aspergillus, *specify in Q.93*
220 Cryptococcus species
230 Fusarium species
240 Mucormycosis (zygomycetes, rhizopus)
250 Yeast, not otherwise specified
259 Other fungus, *specify in Q.93*

3. Viral Infections
301 Herpes Simplex (HSV1, HSV2)
302 Herpes Zoster (Chicken pox, Varicella)
303 Cytomegalovirus (CMV)
304 Adenovirus
305 Enterovirus (Coxsackie, Echo, Polio)
306 Hepatitis A (HAV)
307 Hepatitis B (HBV, Australian antigen)
308 Hepatitis C (HCV)
309 HIV-1 (HTLV-III)
310 Influenza
311 Measles (Rubeola)
312 Mumps
313 Papovavirus
314 Respiratory syncytial virus (RSV)
315 Rubella (German Measles)
316 Parainfluenza
317 Human herpesvirus-6 (HHV-6)
318 Epstein-Barr virus (EBV)
319 Polyomavirus
320 Rotavirus
321 Rhinovirus
329 Other viral, *specify in Q.99*

4. Parasite Infections
401 Pneumocystis (PCP)
402 Toxoplasma
403 Giardia
404 Cryptosporidium
409 Other parasite (amebiasis, echinococcal cyst, trichomonas – either vaginal or gingivitis), *specify in Q.105*

5. Other Infections
501 Suspected atypical bacterial infection
502 Suspected bacterial infection
503 Suspected fungal infection
504 Suspected viral infection
505 Suspected parasite infection
509 No organism identified

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112. Did patient have a history of clinically important <u>fungal</u> infection <u>at any time</u> prior to conditioning for transplant?

1 ☐ Yes ── Specify:
0 ☐ No

    113. Date of onset: ☐☐☐☐☐☐ Month Day Year

    114. Select organism from list on previous page: [F]☐☐

        Other fungus, specify: _____

    115. Select site(s) from list on previous page: ☐☐ **116.** ☐☐

Tests for Serological Evidence of Prior Viral Exposure / Infection

Recipient:	Positive	Negative	Inconclusive	Not Tested
117. HTLV1 antibody	1 ☐	0 ☐	3 ☐	7 ☐
118. Toxoplasma antibody	1 ☐	0 ☐	3 ☐	7 ☐
119. Cytomegalovirus antibody	1 ☐	0 ☐	3 ☐	7 ☐
120. Epstein-Barr antibody	1 ☐	0 ☐	3 ☐	7 ☐
121. Hepatitis B surface and/or core antibody	1 ☐	0 ☐	3 ☐	7 ☐
122. Hepatitis B surface antigen	1 ☐	0 ☐	3 ☐	7 ☐
123. Hepatitis C antibody	1 ☐	0 ☐	3 ☐	7 ☐
124. Hepatitis A antibody	1 ☐	0 ☐	3 ☐	7 ☐
125. Human Immunodeficiency Virus (HIV) antibody	1 ☐	0 ☐	3 ☐	7 ☐

6 ☐ Not able to release information for HIV

High-Dose Therapy (Pretransplant Conditioning)

126. Does protocol for high-dose therapy (conditioning) require some or all agents be given as an inpatient?

Protocol requires:

0 ☐ All agents given as <u>out</u>patient

2 ☐ Some, but not all agents given as <u>in</u>patient

3 ☐ All agents given as <u>in</u>patient

7 ☐ No high dose therapy given

127. Was patient treated in an isolation room during the peri-transplant period?

1 ☐ Yes ── Please specify:
0 ☐ No

             Yes No

    128. 1 ☐ 0 ☐ Conventional private room

    129. 1 ☐ 0 ☐ Laminar air flow room

    130. 1 ☐ 0 ☐ HEPA filtered room

    131. 1 ☐ 0 ☐ Positive pressure

    132. 1 ☐ 0 ☐ Other, specify: _____

133. Date pretransplant conditioning (radiation or drugs) was begun: ☐☐☐☐☐☐ Month Day Year

134. Height at initiation of pretransplant conditioning: ☐☐☐ cm   ☐☐☐ inches

135. Actual weight at initiation of pretransplant conditioning: ☐☐☐ kg   ☐☐☐ pounds

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136. Was irradiation performed as part of the pretransplant conditioning regimen?   1 ☐ Yes   0 ☐ No—— **Go to Q.182**

137. Source of x-ray therapy:
    1 ☐ Linear accelerator—— **138.** Maximum energy: ☐☐☐ MV (million volts)
    2 ☐ ^{60}Co
    7 ☐ Other, specify: _____

139. Calculated mid-line dose-rate during irradiation: ☐☐.☐ cGy (rad)/min

What was the radiation field?

140. **Total Body Radiation**
    1 ☐ Yes——
    0 ☐ No

    141. Total dose: ☐☐☐☐ cGy

    Prescription point:
        Yes No
    142. 1 ☐ 0 ☐ Midline umbilicus
    143. 1 ☐ 0 ☐ Other, specify:_____
    Patient orientation:
        Yes No
    144. 1 ☐ 0 ☐ AP/PA
    145. 1 ☐ 0 ☐ Other, specify:_____
    Method of dose verification:
        Yes No
    146. 1 ☐ 0 ☐ Phantom
    147. 1 ☐ 0 ☐ Diodes on patient
    148. 1 ☐ 0 ☐ Other, specify:_____

    149. Starting date: ☐☐ ☐☐ ☐☐
              Month Day Year

    150. Was radiation fractionated?
        1 ☐ Yes——
        0 ☐ No
        8 ☐ Unknown

        151. Dose per fraction: ☐☐☐☐ cGy
        152. Number of days: ☐☐
        153. Total number of fractions: ☐☐

    154. Was shielding used?
        1 ☐ Yes——
        0 ☐ No
        8 ☐ Unknown

           Yes No
        155. 1 ☐ 0 ☐ Lungs
        156. 1 ☐ 0 ☐ Eyes
        157. 1 ☐ 0 ☐ Liver
        158. 1 ☐ 0 ☐ Kidney
        159. 1 ☐ 0 ☐ Other, specify:
              _____

Radiation field data continued on next page

Radiation field data continued from previous page

160. Total lymphoid or nodal regions 1 ☐ Yes 0 ☐ No

161. Total dose: ☐☐☐☐ cGy **162.** Start date: ☐☐ ☐☐ ☐☐
Month Day Year

163. Was radiation fractionated?
1 ☐ Yes
0 ☐ No
8 ☐ Unknown

164. Dose per fraction: ☐☐☐☐ cGy
165. Number of days: ☐☐
166. Total number of fractions: ☐☐

167. Thoraco-abdominal region 1 ☐ Yes 0 ☐ No

168. Total dose: ☐☐☐☐ cGy **169.** Start date: ☐☐ ☐☐ ☐☐
Month Day Year

170. Was radiation fractionated?
1 ☐ Yes
0 ☐ No
8 ☐ Unknown

171. Dose per fraction: ☐☐☐☐ cGy
172. Number of days: ☐☐
173. Total number of fractions: ☐☐ [Go to Q.182]

182. Was (additional) radiation given to other sites?
1 ☐ Yes
0 ☐ No

183. Was CNS irradiation performed?
1 ☐ Yes
0 ☐ No
184. Dose: ☐☐☐☐ cGy **185.** Start date: ☐☐ ☐☐ ☐☐
Month Day Year

186. Was gonadal irradiation performed?
1 ☐ Yes
0 ☐ No
187. Dose: ☐☐☐☐ cGy **188.** Start date: ☐☐ ☐☐ ☐☐
Month Day Year

189. Was splenic irradiation performed?
1 ☐ Yes
0 ☐ No
190. Dose: ☐☐☐☐ cGy **191.** Start date: ☐☐ ☐☐ ☐☐
Month Day Year

191.[2] Radiation to site of residual tumor?
1 ☐ Yes
0 ☐ No
191.[3] Specify site:_____
191.[4] Dose: ☐☐☐☐ cGy **191.[5]** Start date: ☐☐ ☐☐ ☐☐
Month Day Year

192. Other?
1 ☐ Yes
0 ☐ No
192.[2] Specify site:_____
193. Dose: ☐☐☐☐ cGy **194.** Start date: ☐☐ ☐☐ ☐☐
Month Day Year

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195. Were drugs given for <u>pretransplant</u> conditioning?　1 ☐ Yes　0 ☐ No——[*Go to Q.361*]

196. Date started: ☐☐ ☐☐ ☐☐
Month　Day　Year

	Drug Given Yes　No	Total dose (in mg) pre-marrow infusion (not daily dose)	Number of doses	Continuous infusion ≥24hrs Yes　No	Number of days
197. ALG, ALS, ATG, ATS	1☐ 0☐ **198.**	☐☐☐☐☐	**199.** ☐☐	**200.** 1☐ 0☐	**201.** ☐
202. **Anthracycline**	(1☐ 0☐)				
203. Daunomycin	1☐ 0☐ **204.**	☐☐☐☐☐	**205.** ☐	**206.** 1☐ 0☐	**207.** ☐
208. Doxorubicin (Adriamycin)	1☐ 0☐ **209.**	☐☐☐☐☐	**210.** ☐	**211.** 1☐ 0☐	**212.** ☐
213. Idarubicin	1☐ 0☐ **214.**	☐☐☐☐☐	**215.** ☐	**216.** 1☐ 0☐	**217.** ☐
218. Rubidazone	1☐ 0☐ **219.**	☐☐☐☐☐	**220.** ☐	**221.** 1☐ 0☐	**222.** ☐
223. Other anthracycline, specify:_____	1☐ 0☐ **224.**	☐☐☐☐☐	**225.** ☐	**226.** 1☐ 0☐	**227.** ☐
228. Bleomycin	1☐ 0☐ **229.**	☐☐☐☐☐	**230.** ☐☐	**231.** 1☐ 0☐	**232.** ☐
233. Busulfan (myleran)	1☐ 0☐ **234.**	☐☐☐☐☐	**235.** ☐☐	**236.** 1☐ 0☐	**237.** ☐
238. Carboplatin	1☐ 0☐ **239.**	☐☐☐☐☐	**240.** ☐	**241.** 1☐ 0☐	**242.** ☐
243. Cisplatin	1☐ 0☐ **244.**	☐☐☐☐☐	**245.** ☐☐	**246.** 1☐ 0☐	**247.** ☐
248. **Corticosteroids** (excluding antinausea medication)	(1☐ 0☐)				
249. Methylprednisolone (Solumedrol)	1☐ 0☐				
(**250.** ☐ Oral ☐ IV) **251.**		☐☐☐☐☐	**252.** ☐☐	**253.** 1☐ 0☐	**254.** ☐
255. Prednisone	1☐ 0☐ **256.**	☐☐☐☐☐	**257.** ☐☐	**258.** 1☐ 0☐	**259.** ☐
260. Dexamethasone	1☐ 0☐ **261.**	☐☐☐☐☐	**262.** ☐☐	**263.** 1☐ 0☐	**264.** ☐
265. Other corticosteroids, specify:_____	1☐ 0☐ **266.**	☐☐☐☐☐	**267.** ☐☐	**268.** 1☐ 0☐	**269.** ☐
270. Cyclophosphamide	1☐ 0☐ **271.**	☐☐☐☐☐	**272.** ☐☐	**273.** 1☐ 0☐	**274.** ☐
275. Cytarabine (Ara-C)	1☐ 0☐ **276.**	☐☐☐☐☐	**277.** ☐☐	**278.** 1☐ 0☐	**279.** ☐
280. Etoposide (VP16)	1☐ 0☐ **281.**	☐☐☐☐☐	**282.** ☐☐	**283.** 1☐ 0☐	**284.** ☐
284.² Fludarabine	1☐ 0☐ **284.³**	☐☐☐☐☐	**284.⁴** ☐☐	**284.⁵** 1☐ 0☐	**284.⁶** ☐
285. Ifosfamide	1☐ 0☐ **286.**	☐☐☐☐☐	**287.** ☐☐	**288.** 1☐ 0☐	**289.** ☐

Continued on next page

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Continued from previous page

		Drug Given Yes No	Total dose (in mg) pre-marrow infusion (not daily dose)		Number of doses		Continuous infusion ≥24hrs Yes No		Number of days
290.	Intrathecal chemotherapy	1▢ 0▢							
	291. Cytarabine	1▢ 0▢ 292.	▢▢▢▢▢	293.	▢▢			294.	▢
	295. Methotrexate	1▢ 0▢ 296.	▢▢▢▢▢	297.	▢▢			298.	▢
	299. Other, specify: _____	1▢ 0▢ 300.	▢▢▢▢▢	301.	▢▢			302.	▢
303.	Melphalan (L-PAM)	1▢ 0▢							
	304. ▢ Oral ▢ IV	305.	▢▢▢▢▢	306.	▢▢	307. 1▢ 0▢		308.	▢
309.	Mitoxantrone	1▢ 0▢ 310.	▢▢▢▢▢	311.	▢▢	312. 1▢ 0▢		313.	▢
314.	Monoclonal antibody	1▢ 0▢							
	315. Radionuclide-tagged Mab, specify:_____	1▢ 0▢ 316.	▢▢▢▢▢	317.	▢▢	318. 1▢ 0▢		319.	▢
	320. Campath	1▢ 0▢ 321.	▢▢▢▢▢	322.	▢▢	323. 1▢ 0▢		324.	▢
	325. Other Mab, specify:_____	1▢ 0▢ 326.	▢▢▢▢▢	327.	▢▢	328. 1▢ 0▢		329.	▢
330.	Nitrosourea	1▢ 0▢							
	331. BCNU	1▢ 0▢ 332.	▢▢▢▢▢	333.	▢▢	334. 1▢ 0▢		335.	▢
	336. CCNU	1▢ 0▢ 337.	▢▢▢▢▢	338.	▢▢	339. 1▢ 0▢		340.	▢
	341. Other nitrosourea, specify:_____	1▢ 0▢ 342.	▢▢▢▢▢	343.	▢▢	344. 1▢ 0▢		345.	▢
345.[2]	Paclitaxel (Taxol)	1▢ 0▢ 345.[3]	▢▢▢▢▢	345.[4]	▢▢	345.[5] 1▢ 0▢		355.[6]	▢
346.	Teniposide (VM26)	1▢ 0▢ 347.	▢▢▢▢▢	348.	▢▢	349. 1▢ 0▢		350.	▢
351.	Thiotepa	1▢ 0▢ 352.	▢▢▢▢▢	353.	▢▢	354. 1▢ 0▢		355.	▢
356.	Other, specify: _____	1▢ 0▢ 357.	▢▢▢▢▢	358.	▢▢	359. 1▢ 0▢		360.	▢

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361. Was this the first transplant for this recipient?

1 ☐ Yes ——— **362.** Is a second transplant planned as part of treatment protocol? 1 ☐ Yes 0 ☐ No

0 ☐ No ——— (Go to Q.384)

Previous Transplants

363. Number of <u>previous</u> transplants recipient has had: ☐☐

(if more than 1 <u>previous</u> transplant, photocopy this page and answer Q.364–383 for each <u>previous</u> transplant)

364. Date of <u>previous</u> transplant: ☐☐ ☐☐ ☐☐
Month Day Year

364.² Was <u>previous</u> transplant performed at a different institution?

1 ☐ Yes ———
0 ☐ No

Name: _____
City: _____ State: _____
Country: _____

365. Graft type of <u>previous</u> transplant:

1 ☐ Autologous ———

	Yes	No	
366.	1 ☐	0 ☐	Bone marrow
367.	1 ☐	0 ☐	Peripheral blood
368.	1 ☐	0 ☐	Other, specify: _____

369. Was this transplant reported to the ABMTR?
1 ☐ Yes
0 ☐ No
8 ☐ Unknown

2 ☐ Allogeneic, unrelated donor

370. Same donor as current transplant? 1 ☐ Yes 0 ☐ No

	Yes	No	
371.	1 ☐	0 ☐	Bone marrow
372.	1 ☐	0 ☐	Peripheral blood
373.	1 ☐	0 ☐	Cord Blood
374.	1 ☐	0 ☐	Fetal tissue
375.	1 ☐	0 ☐	Other, specify: _____

3 ☐ Allogeneic, related donor

376. Was this transplant reported to the IBMTR?
1 ☐ Yes
0 ☐ No
8 ☐ Unknown

383. Reason for re-transplant:

1 ☐ No engraftment

2 ☐ Partial engraftment

3 ☐ Graft failure/rejection ——— Date of rejection/failure: ☐☐ ☐☐ ☐☐
Month Day Year

4 ☐ Persistent malignancy

5 ☐ Recurrent malignancy ——— Date of relapse: ☐☐ ☐☐ ☐☐
Month Day Year

6 ☐ Planned second transplant, per protocol

8 ☐ Secondary malignancy (specify disease from lists on pg 2-4): ☐☐☐

90 ☐ Other, specify: _____

Please complete disease-specific insert for secondary malignancy and continue as well with disease insert for disease of first transplant.

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384. What type of graft did patient receive for the current transplant?

1 ☐ Autologous—

385. From where were stem cells obtained?
  1 ☐ Bone marrow——— [*Complete INSERT* **AUTOBM**]
  2 ☐ Blood——— [*Complete INSERT* **AUTOPB**]
  3 ☐ Bone marrow & Blood— [*Complete INSERTS* **AUTOBM & AUTOPB**]

2 ☐ Allogeneic—

3 ☐ Syngeneic—

Yes No
  1 ☐ 0 ☐ Bone marrow —— [*If yes, complete INSERT* **ALLOBM**]
  1 ☐ 0 ☐ Peripheral blood—— [*If yes, complete INSERT* **ALLOPB**]
  1 ☐ 0 ☐ Umbilical cord blood—— [*If yes, complete INSERT* **ALLOCB**]
  1 ☐ 0 ☐ Fetal tissue—— [*If yes, complete INSERT* **ALLOBM**]
  1 ☐ 0 ☐ Other,—— [*If yes, complete INSERT* **ALLOBM**]
        specify:_____

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Posttransplant Information

387. Did patient die prior to day 100 after this transplant?

  1 ❑ Yes – *Answers on pages 19-37 should reflect clinical status immediately prior to death, if no further infusions*

  0 ❑ No – *Answers on pages 19-37 should reflect clinical status on day of actual contact
          for this follow-up examination (approximately 100 days posttransplant), if no further infusions*

388. Did patient receive a subsequent blood or marrow infusion after the transplant for which this report is being completed? (other than peripheral blood leukocytes or T-lymphocytes from original allogeneic donor)

  1 ❑ Yes
  0 ❑ No

Subsequent transplant

Answers on pages 19-37 of this report should reflect clinical status immediately prior to start of conditioning for subsequent infusion.
  ***A separate report covering the subsequent transplant must be submitted unless the
    subsequent transplant is autologous for treatment of graft failure posttransplant.***

389. Date of subsequent infusion: [ ] [ ] [ ] [ ] [ ] [ ]
                                   Month   Day   Year

390. Reason for subsequent infusion:
  1 ❑ No engraftment ————————┐
  2 ❑ Partial engraftment ————┤ *Autologous re-infusions for these reasons do not require separate report completion*
  3 ❑ Late graft failure ————————┘

  4 ❑ Persistent malignancy
  5 ❑ Relapse
  6 ❑ Planned second transplant, per protocol
  8 ❑ Secondary malignancy ———————— *Complete new malignancy Q.864-878*

  90 ❑ Other, specify:_____

391. Type of graft:
  1 ❑ Allogeneic, related ———————┐
  2 ❑ Allogeneic, unrelated ————————┤
  3 ❑ Autologous

  Donor:
  1 ❑ Same donor
  2 ❑ Different donor
  3 ❑ Not applicable, initial transplant was autologous

Source of cells:
392. 1 ❑ Fresh
      2 ❑ Cryopreserved

393. Check all that apply:
     Yes No
     1 ❑ 0 ❑ Bone marrow
     1 ❑ 0 ❑ Peripheral blood
     1 ❑ 0 ❑ Cord blood
     1 ❑ 0 ❑ Fetal tissue
     1 ❑ 0 ❑ Other, specify:_____

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395. Has patient received an infusion of peripheral blood leukocytes or T-lymphocytes from the original donor?

1 ☐ Yes

0 ☐ No

396. Date first infusion given: [ ][ ] [ ][ ] [ ][ ]
    Month   Day   Year

397. Patient weight within 2 weeks of first infusion: [ ][ ] kg   [ ][ ][ ] pounds

398. Total number of infusions: [ ][ ]

399. Total dose of mononuclear cells given: [ ][ ][ ] . [ ] x 10 [ ][ ] (supply exponent)

400. Were cells manipulated prior to infusion?

1 ☐ Yes

0 ☐ No

401. Indicate method:

Yes   No

1 ☐ 0 ☐ T-cell depletion

1 ☐ 0 ☐ CD34 selection

1 ☐ 0 ☐ Incubated with cytokines

1 ☐ 0 ☐ Other, specify:_____

402. Indication for the infusion(s) of donor cells:

1 ☐ Prophylaxis against B-cell lymphoproliferative disorder (or viral infection)

2 ☐ Prophylaxis against relapse

3 ☐ Treatment of relapse

4 ☐ Treatment of B-cell lymphoproliferative disorder

5 ☐ Treatment of viral infection, specify: _____

6 ☐ Graft failure

7 ☐ Other, specify: _____

If answers 3-7 were selected, then answers on pages 19-37 should reflect clinical status immediately prior to infusion. **This is considered a transplant and a separate report covering this infusion and post-infusion events must be submitted.**

Hematopoietic Reconstitution Posttransplant

403. Has patient received hematopoietic growth factors or cytokines post conditioning? 1 ☐ Yes 0 ☐ No—(**Go to Q.481**)

1st course:

		Yes	No		Date Started Month Day Year		Date Stopped Month Day Year	Still Receiving	Indication Code
G-CSF	404.	1 ☐	0 ☐	405.		406.		☐	
GM-CSF	407.	2 ☐	0 ☐	408.		409.		☐	
Erythropoietin	409.²	3 ☐	0 ☐	409.³		409.⁴		☐	
Thrombopoietin	409.⁵	4 ☐	0 ☐	409.⁶		409.⁷		☐	
Interleukin-2	409.⁸	5 ☐	0 ☐	409.⁹		409.¹⁰		☐	
Interleukin-3	410.	6 ☐	0 ☐	411.		412.		☐	
Interleukin-6	413.	7 ☐	0 ☐	414.		415.		☐	
PIXY-321	416.	8 ☐	0 ☐	417.		418.		☐	
Stem Cell Factor (SCF)	419.	9 ☐	0 ☐	420.		421.		☐	
Interferon-alpha	421.²	10 ☐	0 ☐	421.³		421.⁴		☐	
Interferon-gamma	421.⁵	11 ☐	0 ☐	421.⁶		421.⁷		☐	
Blinded growth factor trial, specify agent(s) being studied:_____	422.	89 ☐	0 ☐	423.		424.		☐	
Other, specify:	425.	90 ☐	0 ☐	426.		427.		☐	☐

_____

2nd course:

		Yes	No		Date Started Month Day Year		Date Stopped Month Day Year	Still Receiving	Indication Code
G-CSF	428.	1 ☐	0 ☐	429.		430.		☐	431.
GM-CSF	432.	2 ☐	0 ☐	433.		434.		☐	435.
Erythropoietin	436.	3 ☐	0 ☐	437.		438.		☐	439.
Thrombopoietin	440.	4 ☐	0 ☐	441.		442.		☐	443.
Interleukin-2	444.	5 ☐	0 ☐	445.		446.		☐	447.
Interleukin-3	448.	6 ☐	0 ☐	449.		450.		☐	451.
Interleukin-6	452.	7 ☐	0 ☐	453.		454.		☐	455.
PIXY-321	456.	8 ☐	0 ☐	457.		458.		☐	459.
Stem Cell Factor (SCF)	460.	9 ☐	0 ☐	461.		462.		☐	463.
Interferon-alpha	464.	10 ☐	0 ☐	465.		466.		☐	467.
Interferon-gamma	468.	11 ☐	0 ☐	469.		470.		☐	471.
Blinded growth factor trial, specify agent(s) being studied:_____	472.	89 ☐	0 ☐	473.		474.		☐	475.
Other, specify:	476.	90 ☐	0 ☐	477.		478.		☐	479. ☐

_____

Coding for Indication of Therapy

0. Planned therapy per protocol to promote engraftment
1. Intervention for delay/decline in Absolute Neutrophil Count (ANC)
2. Intervention for delay/decline in platelets
3. Intervention for delay/decline in both ANC and platelets
4. Intervention for delay/decline in red blood cell counts
5. Anti-leukemic or tumor agent to prevent relapse
6. Anti-leukemic or tumor agent to treat relapse
7. Other indication

Continued on next page

Continued from previous page

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480. Did patient receive other courses of growth factors or cytokines posttransplant?

   1 ☐ Yes——⟨ *Photocopy Q.428-479 and answer for each additional course given.* ⟩

   0 ☐ No

   8 ☐ Unknown

Granulopoiesis

481. Is (was) there evidence of hematopoietic recovery following the initial hematopoietic cell infusion? *(check only one)*

   1 ☐ Yes,
      ANC ≥ 500/mm³
      achieved and
      sustained for 3
      consecutive days——

> **482.** Date ANC ≥ 500/mm³ *(First of 3 consecutive days)*: ☐☐☐☐
>   Month Day
>
> **483.** Was ANC ≥ 1000/mm³ achieved and sustained for 3 consecutive days?
>
>   1 ☐ Yes——
> > **484.** Date achieved (first of 3 consecutive days):
> >   ☐☐☐☐☐☐ ☐ Date unknown
> >   Month Day Year
>
>   0 ☐ No
>
>   8 ☐ Unknown
>
> ⟨ Go to **Q.512** ⟩

   2 ☐ Yes,
      ANC ≥ 500/mm³
      for 3 consecutive
      days with sub-
      sequent decline in
      ANC to <500/mm³ for
      greater than 3 days——

> **485.** Date ANC ≥ 500/mm³ *(First of 3 consecutive days)*: ☐☐☐☐☐☐
>   Month Day Year
>
> **486.** Was ANC ≥ 1000/mm³ achieved and sustained for 3 consecutive days?
>
>   1 ☐ Yes——
> > **487.** Date achieved (first of 3 consecutive days):
> >   ☐☐☐☐☐☐ ☐ Date unknown
> >   Month Day Year
>
>   0 ☐ No
>
>   8 ☐ Unknown
>
> **488.** Date of decline in ANC to < 500/mm³ for greater than 3 days
>   *(First of 3 days that ANC declined)*: ☐☐☐☐☐☐
>   Month Day Year
>
> **489.** Did patient recover and maintain ANC ≥ 500/mm³ following the decline?
>
>   1 ☐ Yes——
> > **490.** Date of ANC recovery: ☐☐☐☐☐☐
> >   Month Day Year
>
>   0 ☐ No
>
> ⟨ Go to **Q.491** ⟩

   3 ☐ No, ANC ≥ 500/mm³ was not achieved
      and there was no evidence of recurrent disease in the bone marrow——⟨ Go to **Q.491** ⟩

   4 ☐ No, ANC ≥ 500/mm³ was not achieved
      and there was documented persistent disease in the bone marrow posttransplant——⟨ Go to **Q.491** ⟩

   7 ☐ ANC never dropped below 500/mm³ ——⟨ Go to **Q.512** ⟩

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Suspected etiology of failure to achieve ANC $\geq$ 500/mm³ or of a decline in ANC:

491. Persistent disease or relapse:
- 1 ☐ Yes
- 0 ☐ No
- 8 ☐ Unknown

492. Graft versus host disease:
- 1 ☐ Yes
- 0 ☐ No
- 8 ☐ Unknown

493. Immune-mediated rejection:
- 1 ☐ Yes
- 0 ☐ No
- 8 ☐ Unknown

494. Non-viral infection:
- 1 ☐ Yes
- 0 ☐ No
- 8 ☐ Unknown

495. Suspected viral infection:
- 1 ☐ Yes
- 0 ☐ No
- 8 ☐ Unknown

Virus suspected:

	Yes	No	
496.	1 ☐	0 ☐	Cytomegalovirus (CMV)
497.	1 ☐	0 ☐	Human Herpes Virus Type 6 (HHV6)
498.	1 ☐	0 ☐	Herpes Simplex Virus (HSV)
499.	1 ☐	0 ☐	Varicella
500.	1 ☐	0 ☐	Other, specify: _____

501. Documented viral infection:
- 1 ☐ Yes
- 0 ☐ No
- 8 ☐ Unknown

Virus involved:

	Yes	No	
502.	1 ☐	0 ☐	Cytomegalovirus (CMV)
503.	1 ☐	0 ☐	Human Herpes Virus Type 6 (HHV6)
504.	1 ☐	0 ☐	Herpes Simplex Virus (HSV)
505.	1 ☐	0 ☐	Varicella
506.	1 ☐	0 ☐	Other, specify: _____

507. Drugs:
- 1 ☐ Yes
- 0 ☐ No
- 8 ☐ Unknown

Specify:

	Yes	No	
508.	1 ☐	0 ☐	Ganciclovir
509.	1 ☐	0 ☐	Bactrim, Septra, Trimethoprim-sulfamethoxazole
510.	1 ☐	0 ☐	Other, specify: _____

511. Etiology undetermined:
- 1 ☐ Yes
- 0 ☐ No

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Megakaryopoiesis

The following questions relate to __initial__ platelet recovery. All dates should reflect no transfusions in previous 7 days, and the first of 3 consecutive laboratory results.

512. Was a platelet count of $\geq 20 \times 10^9/L$ achieved?

    1 ☐ Yes ─────────────┐

    0 ☐ No ──────────┐

    7 ☐ Never dropped below 20   **Go to Q.518**

    8 ☐ Unknown ──────┘

513. Date platelets $\geq 20 \times 10^9/L$: ☐☐ ☐☐ ☐☐
        ☐ Date estimated   Month   Day   Year
        ☐ Date unknown

514. Was a platelet count of $\geq 50 \times 10^9/L$ achieved?

    1 ☐ Yes ─────────────┐

    0 ☐ No ──────────┐

    7 ☐ Never dropped below 50   **Go to Q.518**

    8 ☐ Unknown ──────┘

515. Date platelets $\geq 50 \times 10^9/L$: ☐☐ ☐☐ ☐☐
        ☐ Date estimated   Month   Day   Year
        ☐ Date unknown

516. Was a platelet count of $\geq 100 \times 10^9/L$ achieved?

    1 ☐ Yes ─────────────┐

    0 ☐ No

    8 ☐ Unknown

517. Date platelets $\geq 100 \times 10^9/L$: ☐☐ ☐☐ ☐☐
        ☐ Date estimated   Month   Day   Year
        ☐ Date unknown

518. Was patient ever platelet transfusion independent?

    1 ☐ Yes ─────────────┐

    0 ☐ No

    8 ☐ Unknown

    7 ☐ Not applicable (never dependent)

519. Date of last (most recent) platelet transfusion*: ☐☐ ☐☐ ☐☐
        ☐ Date unknown   Month   Day   Year

    * If patient was platelet transfusion independent for ≥ 14 days but subsequently experienced a decline in platelet count and required platelet transfusions, record date of last platelet transfusion __before decline in counts__. If patient has not required platelet transfusions since initial date of recovery, record date of last platelet transfusion.

520. Did patient receive platelet transfusions within 7 days of last contact/death?

    1 ☐ Yes

    0 ☐ No

    8 ☐ Unknown

Erythropoiesis

521. Was patient ever red blood cell (RBC) transfusions independent?

    1 ☐ Yes ─────────────┐

    0 ☐ No

522. Date of last (most recent) RBC transfusion*: ☐☐ ☐☐ ☐☐
        ☐ Date unknown   Month   Day   Year

    * If patient was RBC transfusion independent for ≥ 1 month but subsequently experienced a decline in RBC count and required RBC transfusions, record date of last RBC transfusion __before decline in counts__. If patient has not required RBC transfusions since initial date of recovery, record date of last RBC transfusion.

523. Did patient receive RBC transfusions within 1 month of last contact/death?

    1 ☐ Yes

    0 ☐ No

    8 ☐ Unknown

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Current Hematologic Findings

Date of most recent CBC: . □□ □□ □□□
Month Day Year

Actual CBC results

		Specify Units	Transfused	Not Tested
WBC:	□□□□□□□ . □	1 □ x10⁹/L 2 □ x10⁶/L		□
Neutrophils:	□□ %			□
Lymphocytes:	□□ %			□
Hemoglobin:	□□□□ . □□	1 □ g/dL 2 □ g/L 3 □ mmol/L	□	□
Hematocrit:	□□ %		□	□
Platelets:	□□□□□□	1 □ x10⁹/L 2 □ x10⁶/L	□	□

Acute Graft-vs-Host Disease (GVHD)

524. Was specific therapy used posttransplant to prevent <u>or induce</u> acute GVHD, or promote engraftment (other than growth factors reported in **Q.403**)?

1 □ Yes
0 □ No
8 □ Unknown

Allografts:
Go to **Q.541**

Autografts:
Go to **Q.680**

For each agent listed below indicate whether or not it was used to prevent or induce acute GVHD:

	Yes No	
525.	1 □ 0 □	Methotrexate
526.	1 □ 0 □	Cyclosporine
527.	1 □ 0 □	FK 506 (Tacrolimus)
528.	1 □ 0 □	Corticosteroids
529.	1 □ 0 □	ALS, ALG, ATS, ATG
530.	1 □ 0 □	Azathioprine
531.	1 □ 0 □	Cyclophosphamide
532.	1 □ 0 □	In vivo anti T-lymphocyte monoclonal antibody

	Yes No	
533.	1 □ 0 □	Anti IL-2
534.	1 □ 0 □	Anti CD 25
535.	1 □ 0 □	Campath
536.	1 □ 0 □	OKT3
537.	1 □ 0 □	Other, specify: _____

538. 1 □ 0 □ In vivo immunotoxin, specify: _____

539. 1 □ 0 □ Blinded randomized trial; specify agent being studied: _____

540. 1 □ 0 □ Other, specify: _____

541. Did acute GVHD occur?

1 ☐ Yes ───────────────────────────────────┐
2 ☐ Acute GVHD persists from prior transplant/infusion ──┤
0 ☐ No ─────────────────┐   │
8 ☐ Unknown ──── Go to **Q.593** │   │

542. Maximum overall grade: 1 ☐ I   2 ☐ II   3 ☐ III   4 ☐ IV

What was diagnosis based on?

543. Histologic evidence:

1 ☐ Yes ─────────

0 ☐ No

Sites:

	Yes	No	
544.	1 ☐	0 ☐	Skin
545.	1 ☐	0 ☐	Gut
546.	1 ☐	0 ☐	Liver
547.	1 ☐	0 ☐	Other, specify: _____

548. Clinical evidence:

1 ☐ Yes

0 ☐ No

549. Date of onset: ☐☐ ☐☐ ☐☐
　　　　　　　　　　Month　Day　Year

550. Was acute GVHD still present at time of this report?

1 ☐ Yes
0 ☐ No
2 ☐ Progressed to chronic GVHD
8 ☐ Unknown

List the maximum severity of organ involvement attributed to acute GVHD:

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
551. Skin:	1 ☐ No rash	2 ☐ Maculopapular rash, <25% of body surface	3 ☐ Maculopapular rash, 25–50% of body surface	4 ☐ Generalized erythroderma	5 ☐ Generalized erythroderma with bullae formation and desquamation

552. Intestinal tract (use ml/day for adult patients and ml/m²/day for pediatric patients):

0 ☐ No diarrhea 1 ☐ Diarrhea ≤500 ml/day or <280 ml/m²/day	2 ☐ Diarrhea >500 but ≤1000 ml/day or 280-555 ml/m²/day	3 ☐ Diarrhea >1000 but ≤1500 ml/day or 556-833 ml/m²/day	4 ☐ Diarrhea >1500 ml/day or >833 ml/m²/day	5 ☐ Severe abdominal pain, with or without ileus

553. Liver:

1 ☐ Bilirubin <2.0 mg/dL or <35 μmol/L	2 ☐ Bilirubin 2.0-3.0 mg/dL or 35-52 μmol/L	3 ☐ Bilirubin 3.1-6.0 mg/dL or 53-103 μmol/L	4 ☐ Bilirubin 6.1-15.0 mg/dL or 104-256 μmol/L	5 ☐ Bilirubin >15.0 mg/dL or >256 μmol/L

554. Other organ involvement?

1 ☐ Yes ─────────

0 ☐ No

	Yes	No	
555.	1 ☐	0 ☐	Upper GI tract
556.	1 ☐	0 ☐	Lung
557.	1 ☐	0 ☐	Other, specify: _____

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558. Was specific therapy used to **treat** acute GVHD?   1 ☐ Yes   0 ☐ No——[Go to **Q.593**]

For each agent listed below indicate whether or not it was used to **treat** acute GVHD:

		No, drug not given	Drug continued at prophylactic dose	Yes, drug started	Yes, dose increased		Still taking? Yes No
559.	Methotrexate	0 ☐	1 ☐	2 ☐	3 ☐	**560.**	1 ☐ 0 ☐
561.	Cyclosporine	0 ☐	1 ☐	2 ☐	3 ☐	**562.**	1 ☐ 0 ☐
563.	FK 506 (Tacrolimus)	0 ☐	1 ☐	2 ☐	3 ☐	**564.**	1 ☐ 0 ☐
565.	Systemic Corticosteroids	0 ☐	1 ☐	2 ☐	3 ☐	**566.**	1 ☐ 0 ☐
567.	Topical Corticosteroids	0 ☐	1 ☐	2 ☐	3 ☐	**568.**	1 ☐ 0 ☐
569.	ALS, ALG, ATS, ATG	0 ☐	1 ☐	2 ☐	3 ☐	**570.**	1 ☐ 0 ☐
571.	Azathioprine	0 ☐	1 ☐	2 ☐	3 ☐	**572.**	1 ☐ 0 ☐
573.	Cyclophosphamide	0 ☐	1 ☐	2 ☐	3 ☐	**574.**	1 ☐ 0 ☐
575.	Thalidomide	0 ☐	1 ☐	2 ☐	3 ☐	**576.**	1 ☐ 0 ☐

In vivo anti-T-lymphocyte monoclonal antibody:

		No, drug not given	Drug continued at prophylactic dose	Yes, drug started	Yes, dose increased		Still taking? Yes No
577.	Anti IL-2	0 ☐	1 ☐	2 ☐	3 ☐	**578.**	1 ☐ 0 ☐
579.	Anti CD 25	0 ☐	1 ☐	2 ☐	3 ☐	**580.**	1 ☐ 0 ☐
581.	Campath	0 ☐	1 ☐	2 ☐	3 ☐	**582.**	1 ☐ 0 ☐
583.	OKT3	0 ☐	1 ☐	2 ☐	3 ☐	**584.**	1 ☐ 0 ☐
585.	Other, specify:_____	0 ☐	1 ☐	2 ☐	3 ☐	**586.**	1 ☐ 0 ☐
587.	In vivo immunotoxin, specify:_____	0 ☐	1 ☐	2 ☐	3 ☐	**588.**	1 ☐ 0 ☐
589.	Blinded randomized trial; specify agent being studied:_____	0 ☐	1 ☐	2 ☐	3 ☐	**590.**	1 ☐ 0 ☐
591.	Other, specify:_____	0 ☐	1 ☐	2 ☐	3 ☐	**592.**	1 ☐ 0 ☐

Chronic Graft-vs-Host Disease (GVHD)

593. Has patient developed clinical chronic GVHD?

1 ☐ Yes

0 ☐ No ──── Go to **Q.680**

8 ☐ Unknown

594. Date of onset: ☐☐ ☐☐ ☐☐   ☐ Date unknown
      Month Day Year

595. Progressed from acute GVHD?
      1 ☐ Yes
      0 ☐ No

596. Karnofsky/Lansky score (see page 5) at diagnosis of chronic GVHD: ☐☐☐

597. Platelet count at diagnosis of chronic GVHD: ☐☐☐☐.☐ x 10⁹/L

598. Total serum bilirubin at diagnosis of chronic GVHD: ☐☐.☐

599. Units for bilirubin:
      1 ☐ mg/dL 2 ☐ µmol/L

What was diagnosis based on?

600. Histologic evidence:
      1 ☐ Yes
      0 ☐ No

Sites:

	Yes	No	
601.	1 ☐	0 ☐	Skin
602.	1 ☐	0 ☐	Gut
603.	1 ☐	0 ☐	Liver
604.	1 ☐	0 ☐	Buccal mucosa/lip
605.	1 ☐	0 ☐	Conjunctiva
606.	1 ☐	0 ☐	Lung
607.	1 ☐	0 ☐	Muscle
608.	1 ☐	0 ☐	Other, specify: _____

609. Clinical evidence:
      1 ☐ Yes
      0 ☐ No

610. Maximum grade of chronic GVHD:
      1 ☐ Limited *(Localized skin involvement and/or hepatic dysfunction due to chronic GVHD)*
      2 ☐ Extensive *(Generalized skin involvement; or localized skin involvement and/or hepatic dysfunction
         due to chronic GVHD, plus :
         -Liver histology showing chronic aggressive hepatitis, bridging necrosis or cirrhosis; or,
         -Involvement of eye: Schirmer's test with < 5 mm wetting; or,
         -Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy; or,
         -Involvement of any other target organ)*

611. Overall severity: 1 ☐ Mild   2 ☐ Moderate   3 ☐ Severe

Continued on next page

Continued from previous page

Indicate organ involvement with chronic GVHD from list below:

		Absent	Mild	Moderate	Severe	Present, but unknown Severity	Unknown whether Involved	
Skin/Hair:	612.	0☐	3☐	4☐	5☐	6☐	8☐	Subclinical (biopsy findings only)
	613.	0☐	3☐	4☐	5☐	6☐	8☐	Rash
	614.	0☐	3☐	4☐	5☐	6☐	8☐	Scleroderma
	615.	0☐	3☐	4☐	5☐	6☐	8☐	Dyspigmentation
	616.	0☐	3☐	4☐	5☐	6☐	8☐	Contractures
	617.	0☐	3☐	4☐	5☐	6☐	8☐	Alopecia
	618.	0☐	3☐	4☐	5☐	6☐	8☐	Other skin/hair involvement, specify:
Eyes:	619.	0☐	3☐	4☐	5☐	6☐	8☐	Dry eyes
	620.	0☐	3☐	4☐	5☐	6☐	8☐	Corneal erosion/conjunctivitis
	621.	0☐	3☐	4☐	5☐	6☐	8☐	Other eye involvement, specify:
Mouth:	622.	0☐	3☐	4☐	5☐	6☐	8☐	Lichenoid changes
	623.	0☐	3☐	4☐	5☐	6☐	8☐	Mucositis/ulcers
	624.	0☐	3☐	4☐	5☐	6☐	8☐	Other mouth involvement, specify:
Lung:	625.	0☐	3☐	4☐	5☐	6☐	8☐	Bronchiolitis obliterans
	626.	0☐	3☐	4☐	5☐	6☐	8☐	Other lung involvement, specify:
GI Tract:	627.	0☐	3☐	4☐	5☐	6☐	8☐	Esophageal involvement
	628.	0☐	3☐	4☐	5☐	6☐	8☐	Chronic nausea/vomiting
	629.	0☐	3☐	4☐	5☐	6☐	8☐	Chronic diarrhea
	630.	0☐	3☐	4☐	5☐	6☐	8☐	Malabsorption
	631.	0☐	3☐	4☐	5☐	6☐	8☐	Other GI tract involvement, specify:
Liver:	632.	0☐	3☐	4☐	5☐	6☐	8☐	Liver involvement, specify:
GU Tract:	633.	0☐	3☐	4☐	5☐	6☐	8☐	Vaginitis/stricture
	634.	0☐	3☐	4☐	5☐	6☐	8☐	Other GU involvement, specify:
Musculoskeletal:	635.	0☐	3☐	4☐	5☐	6☐	8☐	Arthritis
	636.	0☐	3☐	4☐	5☐	6☐	8☐	Myositis
	637.	0☐	3☐	4☐	5☐	6☐	8☐	Myasthenia
	638.	0☐	3☐	4☐	5☐	6☐	8☐	Other musculoskeletal involvement, specify:
Hematologic:	639.	0☐	3☐	4☐	5☐	6☐	8☐	Thrombocytopenia
	640.	0☐	3☐	4☐	5☐	6☐	8☐	Eosinophilia
	641.	0☐	3☐	4☐	5☐	6☐	8☐	Autoantibodies
	642.	0☐	3☐	4☐	5☐	6☐	8☐	Other hematologic involvement, specify:
Other:	643.	0☐	3☐	4☐	5☐	6☐	8☐	Specify: _____

644. Was specific therapy used to __treat__ chronic GVHD? 1 ☐ Yes 0 ☐ No——[Go to *Q.679*]

For each agent listed below indicate whether or not it was used to __treat__ chronic GVHD:

	No, drug not given	Drug continued at prophylactic dose	Yes, drug started	Yes, dose increased		Still taking? Yes	No
645. ALS, ALG, ATS, ATG	0 ☐	1 ☐	2 ☐	3 ☐	**646.**	1 ☐	0 ☐
647. Azathioprine	0 ☐	1 ☐	2 ☐	3 ☐	**648.**	1 ☐	0 ☐
649. Cyclosporine	0 ☐	1 ☐	2 ☐	3 ☐	**650.**	1 ☐	0 ☐
651. FK 506 (Tacrolimus)	0 ☐	1 ☐	2 ☐	3 ☐	**652.**	1 ☐	0 ☐
653. Systemic Corticosteriods	0 ☐	1 ☐	2 ☐	3 ☐	**654.**	1 ☐	0 ☐
655. Topical Corticosteriods	0 ☐	1 ☐	2 ☐	3 ☐	**656.**	1 ☐	0 ☐
657. Cyclophosphamide	0 ☐	1 ☐	2 ☐	3 ☐	**658.**	1 ☐	0 ☐
659. Thalidomide	0 ☐	1 ☐	2 ☐	3 ☐	**660.**	1 ☐	0 ☐

In vivo anti-T-lymphocyte monoclonal antibody:

	No, drug not given	Drug continued at prophylactic dose	Yes, drug started	Yes, dose increased		Still taking? Yes	No
661. Anti IL-2	0 ☐	1 ☐	2 ☐	3 ☐	**662.**	1 ☐	0 ☐
663. Anti CD 25	0 ☐	1 ☐	2 ☐	3 ☐	**664.**	1 ☐	0 ☐
665. Campath	0 ☐	1 ☐	2 ☐	3 ☐	**666.**	1 ☐	0 ☐
667. OKT3	0 ☐	1 ☐	2 ☐	3 ☐	**668.**	1 ☐	0 ☐
669. Other, specify: _____	0 ☐	1 ☐	2 ☐	3 ☐	**670.**	1 ☐	0 ☐
671. In vivo immunotoxin, specify:_____	0 ☐	1 ☐	2 ☐	3 ☐	**672.**	1 ☐	0 ☐
673. Blinded randomized trial; specify agent being studied:_____	0 ☐	1 ☐	2 ☐	3 ☐	**674.**	1 ☐	0 ☐
675. Other, specify: _____	0 ☐	1 ☐	2 ☐	3 ☐	**676.**	1 ☐	0 ☐

677. Is patient still receiving treatment for chronic GVHD?

1 ☐ Yes

0 ☐ No—— **678.** Date last treatment was administered: ☐☐ ☐☐ ☐☐
Month Day Year

679. Is chronic GVHD still present?

1 ☐ Yes

0 ☐ No

2 ☐ No symptoms, but patient still receiving treatment

Other Treatment and Clinical Status After Start of Conditioning

680. Were transfusions given at any time after the start of conditioning to present?

1 ☐ Yes

0 ☐ No

> **Yes No**
>
> **681.** 1 ☐ 0 ☐ Did patient receive only CMV-negative blood products?
>
> **682.** 1 ☐ 0 ☐ Were blood products filtered to remove leukocytes?
>
> **683.** 1 ☐ 0 ☐ Were all transfusions irradiated?
>
> **684.** RBC (from conditioning to 60 days posttransplant): ⬚⬚⬚ Units
>
> **685.** Platelet (from conditioning to 60 days posttransplant):
>
> Single donor ⬚⬚⬚ Number of aphereses
>
> Random donor ⬚⬚⬚ Number of donors
>
> **685.²** Irradiated granulocyte infusions
> (from conditioning to 60 days posttransplant): ⬚⬚⬚ Number of infusions

686. Did patient receive any of the following agents for infection <u>prophylaxis</u> after start of conditioning?

1 ☐ Yes

0 ☐ No

> **Yes No**
>
> **686.²** 1 ☐ 0 ☐ Systemic antibacterial antibiotics
>
> **686.³** 1 ☐ 0 ☐ Nonabsorbable antibiotics
>
> **687.** 1 ☐ 0 ☐ Polyclonal IV gamma globulin (not ATG)
>
> **688.** 1 ☐ 0 ☐ CMV/hyperimmune gamma globulin
>
> **689.** 1 ☐ 0 ☐ IV amphotericin
>
> **690.** 1 ☐ 0 ☐ Fluconazole
>
> **691.** 1 ☐ 0 ☐ Itraconazole
>
> **692.** 1 ☐ 0 ☐ Other systemic antifungal agent, specify: _____
>
> **693.** 1 ☐ 0 ☐ Acyclovir
>
> **694.** 1 ☐ 0 ☐ Ganciclovir (DHPG)
>
> **695.** 1 ☐ 0 ☐ Foscarnet
>
> **696.** 1 ☐ 0 ☐ Other antiviral agent, specify: _____
>
> **697.** 1 ☐ 0 ☐ Trimethoprim-sulfamethoxazole (Bactrim/Septra)
>
> **698.** 1 ☐ 0 ☐ Pentamidine inhaled
>
> **699.** 1 ☐ 0 ☐ Pentamidine IV
>
> **700.** 1 ☐ 0 ☐ Dapsone
>
> **701.** 1 ☐ 0 ☐ Other pneumocystis prophylaxis, specify: _____
>
> **702.** 1 ☐ 0 ☐ Other, specify: _____

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703. Did patient develop clinically significant infection after start of conditioning?   1 ☐ Yes   0 ☐ No

Select site and organism from lists shown on the next page and place number in the appropriate spaces. If more than one site or organism was involved, list one site of infection and organism on the first line; second site and/or organism on second line.

**If more than two infections of any category, check here ☐ and copy page
to provide information on 3rd or subsequent infection (do not report in Q.763-771).**

			Site	Organism	Date of Onset Month Day Year	Did infection resolve? Yes No

704. ☐ Bacterial

Typical   First **705.** ☐☐   **706.** _____   **707.** ☐☐☐☐☐☐   **708.** 1☐ 0☐

Second **709.** ☐☐   **710.** _____   **711.** ☐☐☐☐☐☐   **712.** 1☐ 0☐

Atypical   First **716.** ☐☐   **717.** B☐☐   **718.** ☐☐☐☐☐☐   **719.** 1☐ 0☐

Second **720.** ☐☐   **721.** B☐☐   **722.** ☐☐☐☐☐☐   **723.** 1☐ 0☐

724. Other atypical bacterium, specify: _____

727. ☐ Fungal

First **728.** ☐☐   **729.** F☐☐   **730.** ☐☐☐☐☐☐   **731.** 1☐ 0☐

Second **732.** ☐☐   **733.** F☐☐   **734.** ☐☐☐☐☐☐   **735.** 1☐ 0☐

736. Other fungus, specify: _____

739. ☐ Viral

First **740.** ☐☐   **741.** V☐☐   **742.** ☐☐☐☐☐☐   **743.** 1☐ 0☐

Second **744.** ☐☐   **745.** V☐☐   **746.** ☐☐☐☐☐☐   **747.** 1☐ 0☐

748. Other virus, specify: _____

751. ☐ Parasitic

First **752.** ☐☐   **753.** P☐☐   **754.** ☐☐☐☐☐☐   **755.** 1☐ 0☐

Second **756.** ☐☐   **757.** P☐☐   **758.** ☐☐☐☐☐☐   **759.** 1☐ 0☐

760. Other parasite, specify: _____

763. ☐ Other infections

First **764.** ☐☐   **765.** O☐☐   **766.** ☐☐☐☐☐☐   **767.** 1☐ 0☐

Second **768.** ☐☐   **769.** O☐☐   **770.** ☐☐☐☐☐☐   **771.** 1☐ 0☐

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Codes for Common Sites of Infection

1 Blood/buffy coat
2 Disseminated – generalized, isolated at 3 or more distinct sites
3 *Central Nervous System unspecified*
4 Brain
5 Spinal cord
6 Meninges and CSF
10 *Gastrointestinal Tract unspecified*
11 Lips
12 Tongue, oral cavity and oro-pharynx
13 Esophagus
14 Stomach
15 Gallbladder and biliary tree (not hepatitis), pancreas
16 Small intestine
17 Large intestine
18 Feces/stool
19 Peritoneum
20 Liver
30 *Respiratory unspecified*
31 Upper airway and nasopharynx
32 Laryngitis/larynx
33 Lower respiratory tract (lung)
34 Pleural cavity, pleural fluid
35 Sinuses

40 *Genito-Urinary Tract unspecified*
41 Kidneys, renal pelvis, ureters and bladder
42 Prostate
43 Testes
44 Fallopian tubes, uterus, cervix
45 Vagina
50 *Skin unspecified*
51 Genital area
52 Cellulitis
53 Herpes Zoster
54 Rash, pustules or abscesses not typical of any of the above
60 *Central venous catheter unspecified*
61 Catheter insertion or exit site
62 Catheter tip
70 Eyes
75 Ear
81 Joints
82 Bone marrow
83 Bone cortex (osteomyelitis)
84 Muscle (excluding cardiac)
85 Cardiac (endocardium, myocardium, pericardium)
86 Lymph nodes
87 Spleen

Codes for Commonly Reported Organisms

1. Bacteria (Indicate code for atypical bacteria; list bacterium for non-atypical bacteria in Q.706, 710.)

100 Atypical bacteria, not otherwise specified
101 Coxiella
102 Legionella
103 Leptospira
104 Listeria
105 Mycoplasma
106 Nocardia
107 Rickettsia
110 Tuberculosis, NOS (AFB, acid fast bacillus, Koch bacillus)
111 Typical tuberculosis (TB, Tuberculosis)
112 Mycobacteria (avium, bovium, intracellulare)
113 Chlamydia
119 Other atypical bacteria, *specify in Q.724*

2. Fungal Infections
200 Candida, not otherwise specified
201 Candida albicans
202 Candida krusei
203 Candida parapsilosis
204 Candida tropicalis
205 Torulopsis glabrata (a subspecies of candida)
209 Other Candida, *specify in Q.736*
210 Aspergillus, not otherwise specified
211 Aspergillus flavus
212 Aspergillus fumigatus
213 Aspergillus niger
219 Other Aspergillus, *specify in Q.736*
220 Cryptococcus species
230 Fusarium species
240 Mucormycosis (zygomycetes, rhizopus)
250 Yeast, not otherwise specified
259 Other fungus, *specify in Q.736*

3. Viral Infections
301 Herpes Simplex (HSV1, HSV2)
302 Herpes Zoster (Chicken pox, Varicella)
303 Cytomegalovirus (CMV)
304 Adenovirus
305 Enterovirus (Coxsackie, Echo, Polio)
306 Hepatitis A (HAV)
307 Hepatitis B (HBV, Australian antigen)
308 Hepatitis C (HCV)
309 HIV-1 (HTLV-III)
310 Influenza
311 Measles (Rubeola)
312 Mumps
313 Papovavirus
314 Respiratory syncytial virus (RSV)
315 Rubella (German Measles)
316 Parainfluenza
317 Human herpesvirus-6 (HHV-6)
318 Epstein-Barr virus (EBV)
319 Polyomavirus
320 Rotavirus
321 Rhinovirus
329 Other viral, *specify in Q.748*

4. Parasite Infections
401 Pneumocystis (PCP)
402 Toxoplasma
403 Giardia
404 Cryptosporidium
409 Other parasite (amebiasis, echinococcal cyst, trichomonas – either vaginal or gingivitis), *specify in Q.760*

5. Other Infections
501 Suspected atypical bacterial infection
502 Suspected bacterial infection
503 Suspected fungal infection
504 Suspected viral infection
505 Suspected parasite infection
509 No organism identified

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Pulmonary function

775. Has patient developed interstitial pneumonitis (IPn)? | *Interstitial pneumonitis is characterized by hypoxia and diffuse interstitial infiltrates on chest x-ray not caused by fluid overload.*

   1 ☐ Yes ──┐

   0 ☐ No

776. How many episodes of IPn occurred? ☐

> *Note: If more than one episode of IPn, photocopy this page and complete Q.777-795 for subsequent episode(s).*

777. Date of onset of IPn: ☐☐ ☐☐ ☐☐
                             Month Day Year

778. Were diagnostic tests other than radiographic studies done?

   1 ☐ Yes ──┐

   0 ☐ No

> Diagnosis was evaluated by:
>
>   **Yes No**
> 779. 1 ☐ 0 ☐ Bronchoalveolar lavage
> 780. 1 ☐ 0 ☐ Transbronchial biopsy
> 781. 1 ☐ 0 ☐ Open lung biopsy
> 782. 1 ☐ 0 ☐ Autopsy
> 783. 1 ☐ 0 ☐ Other, specify: _____

784. Was an organism isolated?

   1 ☐ Yes ──┐

   0 ☐ No (idiopathic, or no organism isolated)

> Etiology:
>
>   **Yes No**
> 785. 1 ☐ 0 ☐ Pneumocystis carinii
> 786. 1 ☐ 0 ☐ Aspergillus
> 787. 1 ☐ 0 ☐ Candida
> 787.[2] 1 ☐ 0 ☐ Toxoplasma
> 788. 1 ☐ 0 ☐ Respiratory syncytial virus
> 789. 1 ☐ 0 ☐ Cytomegalovirus
> 790. 1 ☐ 0 ☐ Herpes simplex
> 791. 1 ☐ 0 ☐ Adenovirus
> 792. 1 ☐ 0 ☐ Human herpes virus 6
> 793. 1 ☐ 0 ☐ Other virus, specify: _____
> 794. 1 ☐ 0 ☐ Other, specify: _____

795. Has interstitial pneumonitis resolved?

   1 ☐ Yes

   0 ☐ No

   8 ☐ Unknown

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796. Did patient develop pulmonary abnormalities other than interstitial pneumonitis <u>after start of conditioning</u>?

₁ ☐ Yes
₀ ☐ No

> **797.** Did patient develop Acute Respiratory Distress Syndrome (ARDS)?
>
> ₁ ☐ Yes
> ₀ ☐ No
>
> > **798.** Date of onset of ARDS: ☐☐ ☐☐ ☐☐☐☐
> >   Month Day Year
> >
> > **799.** Were diagnostic tests done?
> >
> > ₁ ☐ Yes
> > ₀ ☐ No
> >
> > > Diagnosis was evaluated by:
> > >
> > > | | **Yes** | **No** | |
> > > |---|---|---|---|
> > > | **800.** | ₁ ☐ | ₀ ☐ | Bronchoalveolar lavage |
> > > | **801.** | ₁ ☐ | ₀ ☐ | Transbronchial biopsy |
> > > | **802.** | ₁ ☐ | ₀ ☐ | Open lung biopsy |
> > > | **803.** | ₁ ☐ | ₀ ☐ | Autopsy |
> > > | **804.** | ₁ ☐ | ₀ ☐ | Other, specify: _____ |
>
> **805.** Did patient develop bronchiolitis obliterans?
>
> ₁ ☐ Yes
> ₀ ☐ No
>
> > **806.** Date of onset: ☐☐ ☐☐ ☐☐☐☐
> >   Month Day Year
> >
> > **807.** Were diagnostic tests done?
> >
> > ₁ ☐ Yes
> > ₀ ☐ No
> >
> > > Diagnosis was evaluated by:
> > >
> > > | | **Yes** | **No** | |
> > > |---|---|---|---|
> > > | **808.** | ₁ ☐ | ₀ ☐ | Bronchoalveolar lavage |
> > > | **809.** | ₁ ☐ | ₀ ☐ | Transbronchial biopsy |
> > > | **810.** | ₁ ☐ | ₀ ☐ | Open lung biopsy |
> > > | **811.** | ₁ ☐ | ₀ ☐ | Autopsy |
> > > | **812.** | ₁ ☐ | ₀ ☐ | Other, specify: _____ |
>
> **813.** Did patient develop pulmonary hemorrhage?
>
> ₁ ☐ Yes
> ₀ ☐ No
>
> > **814.** Date of onset: ☐☐ ☐☐ ☐☐☐☐
> >   Month Day Year
> >
> > **815.** Were diagnostic tests done?
> >
> > ₁ ☐ Yes
> > ₀ ☐ No
> >
> > > Diagnosis was evaluated by:
> > >
> > > | | **Yes** | **No** | |
> > > |---|---|---|---|
> > > | **816.** | ₁ ☐ | ₀ ☐ | Bronchoalveolar lavage |
> > > | **817.** | ₁ ☐ | ₀ ☐ | Transbronchial biopsy |
> > > | **818.** | ₁ ☐ | ₀ ☐ | Open lung biopsy |
> > > | **819.** | ₁ ☐ | ₀ ☐ | Autopsy |
> > > | **820.** | ₁ ☐ | ₀ ☐ | Other, specify: _____ |
>
> **821.** Did patient develop other non-infectious pulmonary abnormalities?
>
> ₁ ☐ Yes
> ₀ ☐ No
>
> > **822.** Specify: _____

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Liver function

Units for bilirubin

823. Patient's maximum total bilirubin
in the first 100 days posttransplant: ☐☐·☐

824. ₁☐ mg/dL ₂☐ μmol/L

825. Date of maximum total bilirubin
in the first 100 days posttransplant: ☐☐ ☐☐ ☐☐
Month Day Year

826. Patient's bilirubin on day of last contact: ☐☐☐·☐
(Refer to page 1 for date, or value
obtained closest to last contact)

827. ₁☐ mg/dL ₂☐ μmol/L

827.² Date of last bilirubin
(if different from last contact): ☐☐ ☐☐ ☐☐
Month Day Year

828. Did patient develop any of the following clinical signs/symptoms of abnormal liver function (excluding GVHD)?

₁☐ Yes
₀☐ No

    Yes No
829. ₁☐ ₀☐ Jaundice
830. ₁☐ ₀☐ Hepatomegaly
831. ₁☐ ₀☐ Right upper quadrant pain
832. ₁☐ ₀☐ Ascites
833. ₁☐ ₀☐ Weight gain (>5%)
834. ₁☐ ₀☐ Other, specify: _____

835. Did patient develop non-infectious liver toxicity after conditioning (excluding GVHD)?

₁☐ Yes
₀☐ No

836. What was the date of onset? ☐☐ ☐☐ ☐☐
                                          Month Day Year

Etiology:
    Yes No
837. ₁☐ ₀☐ Veno-occlusive disease
838. ₁☐ ₀☐ Other, specify: _____
839. ₁☐ ₀☐ Unknown

Diagnosis in *Q.837-839* was confirmed by:
    Yes No Not Done
840. ₁☐ ₀☐   Clinical signs and symptoms (see *Q.828*)
841. ₁☐ ₀☐ ₈☐ Elevated liver enzymes (e.g., Alk Phos, ALT, AST, LDH, GGT)
842. ₁☐ ₀☐ ₈☐ Biopsy
843. ₁☐ ₀☐ ₈☐ Autopsy
844. ₁☐ ₀☐ ₈☐ Ultrasonography
845. ₁☐ ₀☐ ₈☐ Doppler
846. ₁☐ ₀☐   Other, specify: _____

847. Has liver toxicity resolved?
₁☐ Yes
₀☐ No

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848. Did patient develop any other non-infectious clinically significant organ impairment or disorder after conditioning?

1 ☐ Yes

0 ☐ No

	Yes No	
849.	1 ☐ 0 ☐	Renal failure requiring dialysis — If yes, received dialysis: 1 ☐ Yes 0 ☐ No
850.	1 ☐ 0 ☐	Posttransplant microangiopathy/thrombotic thrombocytopenic purpura (TTP)/ hemolytic uremic syndrome (HUS) or similar syndrome
851.	1 ☐ 0 ☐	Hemorrhage, if yes specify site —
856.	1 ☐ 0 ☐	Hemorrhagic cystitis
857.	1 ☐ 0 ☐	Seizures
858.	1 ☐ 0 ☐	Cataracts
859.	1 ☐ 0 ☐	Avascular necrosis
860.	1 ☐ 0 ☐	Hypothyroidism
861.	1 ☐ 0 ☐	Gonadal dysfunction
862.	1 ☐ 0 ☐	Growth hormone deficiency/growth disturbance
863.	1 ☐ 0 ☐	Other, specify: _____

	Yes No	
852.	1 ☐ 0 ☐	CNS
853.	1 ☐ 0 ☐	Upper GI tract
854.	1 ☐ 0 ☐	Lower GI tract
855.	1 ☐ 0 ☐	Other, specify: _____

864. Did a <u>new</u> malignancy, lymphoproliferative or myeloproliferative disorder appear?

1 ☐ Yes

0 ☐ No

864.² Did more than one new malignancy develop?

1 ☐ Yes — *Copy page and answer Q.865-878 for each new malignancy*

0 ☐ No

865. Date of diagnosis: ☐☐ ☐☐ ☐☐
Month Day Year

866. Origin of cells: 1 ☐ Host 2 ☐ Donor 7 ☐ Not tested 8 ☐ Unknown

Diagnosis (**send copy of pathology report/other documentation**):

	Yes No	
867.	1 ☐ 0 ☐	Clonal cytogenetic abnormality without leukemia or MDS
868.	1 ☐ 0 ☐	Acute myeloid leukemia
869.	1 ☐ 0 ☐	Other leukemia, specify: _____
870.	1 ☐ 0 ☐	Myelodysplasia
871.	1 ☐ 0 ☐	Lymphoma or lymphoproliferative disease

872. EBV positive? 1 ☐ Yes 0 ☐ No 8 ☐ Unknown

873.	1 ☐ 0 ☐	Hodgkin disease
875.	1 ☐ 0 ☐	Other cancer

876. Primary site: _____

877. Histologic type: _____

878. Behavior:

1 ☐ Benign

2 ☐ In situ

3 ☐ Malignant/invasive

8 ☐ Unknown

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Survival and Functional Status

879. Was patient discharged from hospital after transplant?

1 ☐ Yes ───────┐
┌──┐
│ 880. Date of first discharge from   ☐☐ ☐☐ ☐☐   │
0 ☐ No │   hospital after transplant: Month Day Year │
└──┘
7 ☐ Not applicable,
    high-dose therapy and transplant/infusion given as outpatient

881. *Autografts only:* Total number inpatient days in first 60 days after start of high-dose therapy: ☐☐

882. *Allografts only:* Total number inpatient days in first 100 days after start of high-dose therapy: ☐☐☐

883. Was patient alive on the day of last contact? (*Refer to page 1 for date*):

1 ☐ Yes ───────┐
┌──┐
│ 884. *If the patient is 16 years of age or older, complete the Karnofsky Scale.* │
0 ☐ No │   *If the patient is younger than 16 years of age, complete the Lansky Scale.* │
└──┘

┌──────────────┐
│ Go to *Q.895* │
└──────────────┘

Karnofsky Scale (age ≥16 yrs)	**Lansky Scale (age <16 yrs)**
Select the phrase in the Karnofsky Scale which best describes the activity status of the patient:	Select the phrase in the Lansky Play-Performance Scale which best describes the activity status of the patient:
Able to carry on normal activity; no special care is needed. ☐100 Normal; no complaints; no evidence of disease ☐ 90 Able to carry on normal activity ☐ 80 Normal activity with effort	**Normal range.** ☐100 Fully active ☐ 90 Minor restriction in physically strenuous play ☐ 80 Restricted in strenuous play, tires more easily, otherwise active
Unable to work; able to live at home, care for most personal needs; a varying amount of assistance is needed. ☐ 70 Cares for self; unable to carry on normal activity or to do active work ☐ 60 Requires occasional assistance but is able to care for most needs ☐ 50 Requires considerable assistance and frequent medical care	**Mild to moderate restriction.** ☐ 70 Both greater restrictions of, and less time spent in, active play ☐ 60 Ambulatory up to 50% of time, limited active play with assistance/supervision ☐ 50 Considerable assistance required for any active play; fully able to engage in quiet play
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly. ☐ 40 Disabled; requires special care and assistance ☐ 30 Severely disabled; hospitalization indicated, although death not imminent ☐ 20 Very sick; hospitalization necessary ☐ 10 Moribund; fatal process progressing rapidly	**Moderate to severe restriction.** ☐ 40 Able to initiate quiet activities ☐ 30 Needs considerable assistance for quiet activity ☐ 20 Limited to very passive activity initiated by others (i.e., TV) ☐ 10 Completely disabled, not even passive play

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*(If patient is alive, answer **Q.885-894**; if dead, skip to **Q.895**)*

885.   Patient (age ≥ 6 years) currently attends school:

₁ ☐ Yes—

₀ ☐ No

> 886.   ₁ ☐ Part-time   ₂ ☐ Full-time   ₈ ☐ Unknown, whether part-time or full-time
>
> 887.   Date returned to school: ☐☐ ☐☐   ☐ Date unknown
>   Month Year

888.   Patient was employed outside the home prior to current illness:

₁ ☐ Yes—

₀ ☐ No

> 889.   Patient has returned to work:
>
> ₁ ☐ Yes—
>
> > 890.   Date returned to work: ☐☐ ☐☐   ☐ Date unknown
> >   Month Year
>
> ₀ ☐ No—
>
> > 891.   Patient able to work but is not employed: ₁☐Yes ₀☐No
>
> ₈ ☐ Unknown

> 892.   Patient has resumed all household activities:
>
> ₁ ☐ Yes—
> ₀ ☐ No
> ₈ ☐ Unknown
>
> > 893.   Date resumed all activities: ☐☐ ☐☐ ☐ Date unknown
> >   Month Year
>
> 894.   Patient is now employed:
>
> ₁ ☐ Yes—
> ₀ ☐ No
> ₈ ☐ Unknown
>
> > 894.²   Date began work: ☐☐ ☐☐   ☐ Date unknown
> >   Month Year

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Death Information

895. Date of death: ☐☐ · ☐☐ · ☐☐
    Month   Day   Year

Cause(s) of death:

Enter appropriate cause of death below.

If a code number for "Other, specify" (codes 29, 39, 88, 89, 109, 129, 900) is entered, write the cause in the space provided.

896. Primary: ☐☐☐ Specify: _____

Contributing or secondary causes:

897. ☐☐☐ Specify: _____

898. ☐☐☐ Specify: _____

899. ☐☐☐ Specify: _____

900. ☐☐☐ Specify: _____

901. ☐☐☐ Specify: _____

Cause of Death Codes*

10 Graft rejection or failure

Infection (other than interstitial pneumonia)
  20 Infection, organism not identified
  21 Bacterial
  22 Fungal
  23 Viral
  24 Protozoal
  29 Other infection, specify

Interstitial pneumonia
  30 IPn, idiopathic
  31 Cytomegalovirus (CMV)
  32 Viral, other
  33 Pneumocystis (PCP)
  34 Fungal
  39 Other IPn, specify

40 Adult Respiratory Distress Syndrome, ARDS
   (other than IPn)

50 Acute GVHD
60 Chronic GVHD

70 Recurrence or persistence of primary disease

   * *NOTE: Code "70" may only be used as a primary cause of death, not a contributing or secondary cause.*

Organ failure (not due to GVHD or infection)
  80 Organ failure, not otherwise specified
  81 Liver (not VOD)
  82 VOD
  83 Cardiac (Cardiomyopathy)
  84 Pulmonary
  85 CNS·
  86 Renal
  87 Gastrointestinal (not liver)
  88 Multiple organ failure, specify
  89 Other organ failure, specify

90 Secondary malignancy

(malignancy other than one for which transplant performed includes post transplant lymphoproliferative disease and MDS)

Hemorrhage
  100 Hemorrhage, not otherwise specified
  101 Pulmonary
  102 Intracranial
  103 Gastrointestinal
  109 Other hemorrhage, specify

110 Accidental death

Vascular
  120 Vascular, not otherwise specified
  121 Thromboembolic
  122 Diffused intrevascular congulation (DIC)
  123 Thrombotic thrombocytopenic purpura
  129 Other vascular, specify

130 In utero death (for in utero transplants)

140 Prior malignancy

(malignancy existing before disease for which transplant performed as reported in Q.41)

900 Other, specify

902. Was cause of death confirmed by autopsy?

1 ☐ Yes
0 ☐ No
8 ☐ Unknown
6 ☐ Pending

Send copy of autopsy report when available
Autopsy included with this report:
   1 ☐ Yes   0 ☐ No

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Confidential/Socioeconomic Information

903. Patient's First Name: ☐☐☐☐☐☐☐☐☐☐

904. Patient's Last Name: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

905. Patient's state of residence (*US only*): ☐☐

906. Zip code for place of patient's <u>residence</u> (*US only*): ☐☐☐☐☐ – ☐☐☐☐

907. Country of residence *(check one)*:

1 ☐ United States	10 ☐ Cuba	18 ☐ India	27 ☐ New Zealand	36 ☐ Switzerland
2 ☐ Argentina	42 ☐ Czech Republic	48 ☐ Iran	28 ☐ Norway	37 ☐ Taiwan
3 ☐ Austria	11 ☐ Denmark	19 ☐ Ireland	50 ☐ Peru	45 ☐ Turkey
4 ☐ Australia	44 ☐ Egypt	20 ☐ Israel	29 ☐ Poland	47 ☐ Uruguay
5 ☐ Belgium	12 ☐ England	21 ☐ Italy	30 ☐ Portugal	39 ☐ Venezuela
41 ☐ Bosnia	13 ☐ Finland	22 ☐ Japan	38 ☐ Russia	40 ☐ Wales
6 ☐ Brazil	14 ☐ France	23 ☐ Jordan	31 ☐ Saudi Arabia	88 ☐ Unknown/Unspecified
7 ☐ Canada	15 ☐ Germany	24 ☐ Korea	32 ☐ Scotland	90 ☐ Other Country
8 ☐ Chile	49 ☐ Greece	25 ☐ Malaysia	33 ☐ South Africa	specify:_____
9 ☐ China	46 ☐ Hong Kong	43 ☐ Mexico	34 ☐ Spain	
51 ☐ Croatia	17 ☐ Hungary	26 ☐ Netherlands	35 ☐ Sweden	

908. Does patient have a US Social Security Number or Canadian Social Insurance Number?

1 ☐ Yes——| **909.** Social Security or Social Insurance Number: ☐☐☐☐☐☐☐☐☐☐☐

0 ☐ No

8 ☐ Unknown

7 ☐ Not applicable

909.² Patient ≥18 years old:

1 ☐ Yes——

0 ☐ No

910. Patient's marital status: (*check one*)
1 ☐ Single, never married
2 ☐ Married
3 ☐ Separated
4 ☐ Divorced
5 ☐ Widowed
8 ☐ Unknown

911. Highest grade patient finished in school:
1 ☐ 1 – 8 grades
2 ☐ 9 – 11 grades
3 ☐ High School graduate
4 ☐ Some college
5 ☐ Junior college degree
6 ☐ College degree (BA/BS)
7 ☐ Some post-college work
8 ☐ Advanced degree
88 ☐ Unknown

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912. Type of health insurance: (*check all that apply*)

☐ No Insurance

☐ Medicaid

☐ Medicare (US)

☐ Disability Insurance

☐ HMO

☐ Individual Health Insurance

☐ Group Health Insurance

☐ National Health Insurance (non-US)

☐ V.A./Military

☐ Other, specify: _____

913. (*U.S. patients only*) Type of fee reimbursement:

1 ☐ Fee for service

2 ☐ Capitation

7 ☐ Other, specify: _____

8 ☐ Unknown

914. Which category best describes patient's occupation?
If not currently employed, which best describes patient's LAST job? (check only one)

1 ☐ Professional, Technical, & Related Occupations (teacher/professor, nurse, lawyer, physician or engineer)

2 ☐ Manager, Administrator or Proprietor (sales manager, real estate agent, or postmaster)

3 ☐ Clerical & Related Occupations (secretary, clerk, or mail carrier)

4 ☐ Sales Occupation (salesperson, demonstrator, agent or broker)

5 ☐ Service Occupation (police, cook or hairdresser)

6 ☐ Skilled crafts & Related Occupations (carpenter, repairer or telephone line worker)

7 ☐ Equipment or Vehicle Operator & Related Occupations (driver, railroad brakeman, or sewer worker)

8 ☐ Laborer (helper, longshoreman or warehouse worker)

9 ☐ Farmer (owner, manager, operator, or tenant)

10 ☐ Member of the military

11 ☐ Homemaker

90 ☐ Other, please describe: _____

88 ☐ Unknown

915. (*US patients only*) What is patient's yearly income, earned by <u>all</u> family members living in household, <u>before taxes</u>?
(*check one*)

1 ☐ Less than $5,000   6 ☐ $40,000 – $49,999

2 ☐ $ 5,000 – $9,999   7 ☐ $50,000 – $59,999

3 ☐ $10,000 – $19,999   8 ☐ $60,000 – $79,999

4 ☐ $20,000 – $29,999   9 ☐ $80,000 and over

5 ☐ $30,000 – $39,999   88 ☐ Unknown

INSTITUTIONAL INFORMATION

TEAM ☐☐☐   IUBMID ☐☐☐☐☐☐

(Institutional Unique Blood or Marrow Transplant Identification Number)

Date of transplant for which this form is being completed: ☐☐ ☐☐ ☐☐
Month   Day   Year

Registry: IBMTR   ABMTR   *(circle one)*

Date of report: ☐☐ ☐☐ ☐☐
Month   Day   Year

---

1. Signed: _____ / _____
   Person completing this form / Please print name

3. Name of doctor for correspondence: _____

   Institution: _____

   Address: _____

   _____

   _____

   Telephone: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐   Ext: ☐☐☐☐

   Fax: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

4. Make reimbursement check payable to: _____
   Payment for data forms is contingent on the availability of funds that have been obtained from sources external to the Medical College of Wisconsin for purposes of these payments.

5. Patient or authorized family member/guardian is aware of, and has consented to, the fact that this case is being entered into the Registry database:
   _____ (physician's initials).

6. Determining cut-off for all parts of this report:

   A complete report of transplant consists of the following three parts (all 3 parts should have the same date of report and date of transplant):

   • A (white) Day 100 CORE form

   • An appropriate (blue or pink) graft-specific insert (Insert ALLOBM, ALLOPB, ALLOCB, AUTOPB, or AUTOBM)

   • An appropriate (ivory) disease-specific insert (Inserts I through XVIII)

   Report Form = | **Day 100 CORE Form** | + | **Graft Insert** | + | **Disease Insert** |

   Enter date 100 days from transplant (e.g., Month, Day, Year): ☐☐ ☐☐ ☐☐

   The cut-off for **ALL** parts of this Report Form should be the date of the follow-up exam approximately 100 days post transplant, unless (a) patient died prior to day 100, or (b) patient received a subsequent transplant or infusion >14 days but <100 days post transplant which requires a separate Report Form. (See pages 17 & 18 of the 100 day CORE Form to determine if the re-infusions is considered another transplant requiring a separate Report Form.)

   The date of Last Contact is the date of the 100 day follow-up exam or (a) the date of death (if death occurred before 100 days) or (b) one day prior to conditioning for subsequent transplant or one day prior to subsequent transplant/ infusion if no conditioning given.

   Enter Last Contact date (e.g., Month, Day, Year): ☐☐ ☐☐ ☐☐

   Enter these dates on page 1 of the CORE Form. Report information in the 100 day CORE Form and disease-specification insert only up to Last Contact date. Later information should be reported in a Follow-up Form or Report Form for a subsequent transplant when it is due.

IBMTR/ABMTR Reporting Form 095-CORE (12/98) VOUCHER

FOLLOW-UP CORE FORM

TEAM ☐☐☐☐   IUBMID ☐☐☐☐☐☐☐
(Institutional Unique Blood or Marrow Transplant Identification Number)

Registry (circle one):   IBMTR   ABMTR

Date of transplant for which this form is being completed: ☐☐ ☐☐ ☐☐
Month   Day   Year

Date of report: ☐☐ ☐☐ ☐☐
Month   Day   Year

Series 095 Reporting Forms
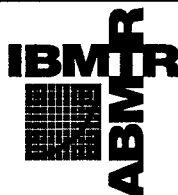
IBMTR / ABMTR

Statistical Center

Medical College of Wisconsin
P.O. Box 26509, 8701 Watertown Plank Road
Milwaukee, WI 53226
▪ Telephone: 414-456-8325 ▪ Fax: 414-456-6530

Follow-up Information

For living patients, submit follow-up data every 12 months from date of transplant. If more than 2 years have elapsed without submitting a Follow-up Report Form, it is only necessary to complete one Follow-up ending with the most recent patient contact. If patient died since last report, indicate findings present at time of death. For patients lost to follow-up since last report, submit last known information. If another infusion was done since last report, see sections at Q.15 and Q.26 of this report to determine if a separate Day 100 Report is required.

2. Patient birthdate: ☐☐ ☐☐ ☐☐☐☐
   Month   Day   Year

3. Date of last actual contact with patient to determine medical status for this report: ☐☐ ☐☐ ☐☐
   (See Q.6 on the COREFU voucher for help determining the cut-off contact date for this report)   Month   Day   Year

Survival and Functional Status

4. Was patient alive on the day of last contact?   1 ☐ Yes   0 ☐ No——[Go to **Q.15**]

> 5. If the patient is 16 years of age or older, complete the Karnofsky Scale.
>   If the patient is younger than 16 years of age, complete the Lansky Scale.

Karnofsky Scale (age ≥16 yrs)	Lansky Scale (age <16 yrs)
Select phrase which best describes activity status:	Select phrase which best describes the activity status:
Able to carry on normal activity; no special care is needed.	**Normal range.**
☐ 100 Normal; no complaints; no evidence of disease	☐ 100 Fully active
☐ 90 Able to carry on normal activity	☐ 90 Minor restriction in physically strenuous play
☐ 80 Normal activity with effort	☐ 80 Restricted in strenuous play, tires more easily, otherwise active
Unable to work; able to live at home, care for most personal needs; a varying amount of assistance is needed.	**Mild to moderate restriction.**
☐ 70 Cares for self; unable to carry on normal activity or to do active work	☐ 70 Both greater restrictions of, and less time spent in, active play
☐ 60 Requires occasional assistance but is able to care for most needs	☐ 60 Ambulatory up to 50% of time, limited active play with assistance/supervision
☐ 50 Requires considerable assistance and frequent medical care	☐ 50 Considerable assistance required for any active play; fully able to engage in quiet play
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	**Moderate to severe restriction.**
☐ 40 Disabled; requires special care and assistance	☐ 40 Able to initiate quiet activities
☐ 30 Severely disabled; hospitalization indicated, although death not imminent	☐ 30 Needs considerable assistance for quiet activity
☐ 20 Very sick; hospitalization necessary	☐ 20 Limited to very passive activity initiated by others (i.e., TV)
☐ 10 Moribund; fatal process progressing rapidly	☐ 10 Completely disabled, not even passive play

TEAM ☐☐☐☐ IUBMID ☐☐☐☐☐☐

6. Is patient (age ≥6 years) currently attending school?

1 ☐ Yes ──────

0 ☐ No

> 7. Specify status: 1 ☐ Part-time 2 ☐ Full-time 8 ☐ Unknown, whether part-time or full-time
>
> 8. Date returned to school: ☐☐ ☐☐ or ☐ Reported previously
>   Month Year

9. Was patient employed outside the home prior to current illness?

1 ☐ Yes

0 ☐ No

10. Has patient been employed outside the home since last report?

1 ☐ Yes ──────

0 ☐ No

> 11. Date returned to work: ☐☐ ☐☐ or ☐ Reported previously
>   Month Year
>
> 12. Patient able to work but is not employed: 1 ☐ Yes 0 ☐ No

8 ☐ Unknown

13. Has patient resumed all household activities?

1 ☐ Yes ──────

0 ☐ No

8 ☐ Unknown

> 14. Approximate date all   ☐☐ ☐☐ or ☐ Reported previously
>   activities were resumed: Month Year

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15. Did patient receive a blood or marrow infusion since the date of last report (*other than peripheral blood leukocytes or T-lymphocytes from original allogeneic donor*)?

1 ☐ Yes
0 ☐ No

Subsequent transplant

Answers to all questions in this report should reflect clinical status immediately prior to start of conditioning for subsequent infusion.
A separate report covering the subsequent transplant must be submitted unless the subsequent transplant is autologous for treatment of graft failure posttransplant.

16. Date of subsequent infusion: ☐☐ ☐☐ ☐☐
        Month   Day   Year

17. Reason for subsequent infusion:
        1 ☐ No engraftment⎯⎯⎯⎯
        2 ☐ Partial engraftment⎯⎯
        3 ☐ Late graft failure⎯⎯⎯

> ***Autologous re-infusions for these reasons do not require separate report completion***

        4 ☐ Persistent malignancy
        5 ☐ Relapse
        6 ☐ Planned second transplant, per protocol
        8 ☐ Secondary malignancy⎯⎯⎯⎯⎯⎯⎯ *Complete new malignancy Q.456-469*
        90 ☐ Other, specify:_____

18. Type of graft:
        1 ☐ Allogeneic, related⎯⎯
        2 ☐ Allogeneic, unrelated⎯
        3 ☐ Autologous

> **19.** Donor:
>   1 ☐ Same donor
>   2 ☐ Different donor
>   3 ☐ Not applicable, initial transplant was autologous

<u>Source of cells:</u>
20. 1 ☐ Fresh
         2 ☐ Cryopreserved

Check all that apply:
<u>Yes</u> <u>No</u>
21. 1 ☐ 0 ☐ Bone marrow
22. 1 ☐ 0 ☐ Peripheral blood
23. 1 ☐ 0 ☐ Cord blood
24. 1 ☐ 0 ☐ Fetal tissue
25. 1 ☐ 0 ☐ Other, specify:_____

TEAM ☐☐☐☐   IUBMID ☐☐☐☐☐☐

26. *Allografts only:* Has patient received an infusion of peripheral blood leukocytes or T-lymphocytes from the original donor since date of last report?

1 ☐ Yes——

0 ☐ No

> **27.** Date first infusion given: ☐☐ ☐☐ ☐☐
>   Month Day Year
>
> **28.** Patient weight within 2 weeks of first infusion: ☐☐ kg ☐☐☐ pounds
>
> **29.** Total number of infusions: ☐☐
>
> **30.** Total dose of mononuclear cells infused: ☐☐☐.☐ x 10 ☐☐ (supply exponent)
>
> **31.** Were cells manipulated prior to infusion?
>   1 ☐ Yes——
>   0 ☐ No
>
> > **32.** Indicate method:
> > **Yes No**
> > 1 ☐ 0 ☐ T-cell depletion
> > 1 ☐ 0 ☐ CD34 selection
> > 1 ☐ 0 ☐ Incubated with cytokines
> > 1 ☐ 0 ☐ Other, specify:_____
>
> **33.** Indication for the infusion(s) of donor cells:
>   1 ☐ Prophylaxis against B-cell lymphoproliferative disorder (or viral infection)
>   2 ☐ Prophylaxis against relapse
>
> > 3 ☐ Treatment of relapse
> > 4 ☐ Treatment of B-cell lymphoproliferative disorder
> > 5 ☐ Treatment of viral infection, specify: _____
> > 6 ☐ Graft failure
> > 7 ☐ Other, specify: _____
>
> > *If answers 3-7 were selected, then answers to all questions in this report should reflect clinical status immediately prior to infusion.*
> > **This is considered a transplant and a separate report covering this infusion and post-infusion events must be submitted.**

Hematopoietic Reconstitution

34. Has patient received hematopoietic growth factors or cytokines since last report? 1 ☐ Yes 0 ☐ No──(*Go to Q.88*)

> **Coding for Indication of Therapy (below)**
> 1. Intervention for delay/decline in Absolute Neutrophil Count (ANC)
> 2. Intervention for delay/decline in platelets
> 3. Intervention for delay/decline in both ANC and platelets
> 4. Intervention for delay/decline in red blood cell counts
> 5. Anti-leukemic or tumor agent to <u>prevent</u> relapse
> 6. Anti-leukemic or tumor agent to <u>treat</u> relapse
> 7. Other indication

Specify agents given:

			Date Started Month Day Year		Date Stopped Month Day Year		Indication
	Yes No						
G-CSF	**35.** 1☐ 0☐	**36.** ☐☐☐☐☐☐		**37.** ☐☐☐☐☐☐			**38.** ☐
GM-CSF	**39.** 1☐ 0☐	**40.** ☐☐☐☐☐☐		**41.** ☐☐☐☐☐☐			**42.** ☐
Erythropoietin	**43.** 1☐ 0☐	**44.** ☐☐☐☐☐☐		**45.** ☐☐☐☐☐☐			**46.** ☐
Thrombopoietin	**47.** 1☐ 0☐	**48.** ☐☐☐☐☐☐		**49.** ☐☐☐☐☐☐			**50.** ☐
Interleukin-2	**51.** 1☐ 0☐	**52.** ☐☐☐☐☐☐		**53.** ☐☐☐☐☐☐			**54.** ☐
Interleukin-3	**55.** 1☐ 0☐	**56.** ☐☐☐☐☐☐		**57.** ☐☐☐☐☐☐			**58.** ☐
Interleukin-6	**59.** 1☐ 0☐	**60.** ☐☐☐☐☐☐		**61.** ☐☐☐☐☐☐			**62.** ☐
PIXY-321	**63.** 1☐ 0☐	**64.** ☐☐☐☐☐☐		**65.** ☐☐☐☐☐☐			**66.** ☐
Stem Cell Factor (SCF)	**67.** 1☐ 0☐	**68.** ☐☐☐☐☐☐		**69.** ☐☐☐☐☐☐			**70.** ☐
Interferon-alpha	**71.** 1☐ 0☐	**72.** ☐☐☐☐☐☐		**73.** ☐☐☐☐☐☐			**74.** ☐
Interferon-gamma	**75.** 1☐ 0☐	**76.** ☐☐☐☐☐☐		**77.** ☐☐☐☐☐☐			**78.** ☐
Blinded growth factor trial, specify agent(s) being studied:	**79.** 1☐ 0☐	**80.** ☐☐☐☐☐☐		**81.** ☐☐☐☐☐☐			**82.** ☐
_____							
Other, specify:	**83.** 1☐ 0☐	**84.** ☐☐☐☐☐☐		**85.** ☐☐☐☐☐☐			**86.** ☐

_____

87. Did patient receive other courses of growth factors or cytokines since last report?

1 ☐ Yes── (*Photocopy Q.35-86 and answer for each additional course given.*)
0 ☐ No
8 ☐ Unknown

NOTE: A <u>new course</u> includes starting a new agent, restarting a previously administered agent for a new indication or restarting a previously administered agent for the same indication but ≥30 days after discontinuing the agent.

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Granulopoiesis

88. Did patient achieve an <u>initial</u> hematopoietic recovery (ANC $\geq$500/mm³ for 3 consecutive days) since last report?

    1 ☐ Yes

> **89.** Date ANC $\geq$500/mm³: [ ][ ][ ][ ][ ][ ]   ☐ Date unknown
> (*First of 3 consecutive days*) Month Day Year
>
> **90.** Was ANC $\geq$1000/mm³ achieved and sustained for 3 consecutive days?
>
>   1 ☐ Yes
>   0 ☐ No
>   [Go to **Q.92**]
>
> > **91.** Date achieved: [ ][ ][ ][ ][ ][ ] ☐ Date unknown
> >   Month Day Year
> > (*First of 3 consecutive days*)

    2 ☐ No, patient's initital hematopoietic recovery was recorded on a previous report———[Go to **Q.92**]

    3 ☐ No, patient has never achieved an ANC $\geq$500/mm³ for
three consecutive days and there is no evidence of recurrent disease———[Go to **Q.92**]

    4 ☐ No, patient has never achieved an ANC $\geq$500/mm³ for three consecutive
days and there was documented persistent malignant disease posttransplant———[Go to **Q.92**]

92. Following initial hematopoietic recovery (ANC $\geq$500/mm³ for three consecutive days) did the patient
experience a subsequent decline in ANC to <500/mm³ for greater than three days <u>since last report</u>?

    1 ☐ Yes
    0 ☐ No
    [Go to **Q.117**]

> **93.** Date of decline in ANC to <500/mm³ [ ][ ][ ][ ][ ][ ] ☐ Date unknown
> for greater than 3 days: Month Day Year
> (*First of 3 days that ANC declined*)
>
> **94.** Did patient recover and maintain ANC $\geq$500/mm³ following the decline?
>
>   1 ☐ Yes
>   0 ☐ No
>   [Go to **Q.96**]
>
> > **95.** Date of ANC recovery: [ ][ ][ ][ ][ ][ ] ☐ Date
> >   Month Day Year unknown

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Suspected etiology of failure to achieve ANC >500/mm³ or of a decline in ANC:

96. Persistent disease or relapse: 1 ☐ Yes 0 ☐ No 8 ☐ Unknown

97. Graft versus host disease: 1 ☐ Yes 0 ☐ No 8 ☐ Unknown

98. Immune-mediated rejection: 1 ☐ Yes 0 ☐ No 8 ☐ Unknown

99. Non-viral infection: 1 ☐ Yes 0 ☐ No 8 ☐ Unknown

100. Suspected viral infection: 1 ☐ Yes 0 ☐ No 8 ☐ Unknown

> Virus suspected:
> **Yes No**
> **101.** 1 ☐ 0 ☐ Cytomegalovirus (CMV)
> **102.** 1 ☐ 0 ☐ Human Herpes Virus Type 6 (HHV6)
> **103.** 1 ☐ 0 ☐ Herpes Simplex Virus (HSV)
> **104.** 1 ☐ 0 ☐ Varicella
> **105.** 1 ☐ 0 ☐ Other, specify: _____

106. Documented viral infection: 1 ☐ Yes 0 ☐ No 8 ☐ Unknown

> Virus involved:
> **Yes No**
> **107.** 1 ☐ 0 ☐ Cytomegalovirus (CMV)
> **108.** 1 ☐ 0 ☐ Human Herpes Virus Type 6 (HHV6)
> **109.** 1 ☐ 0 ☐ Herpes Simplex Virus (HSV)
> **110.** 1 ☐ 0 ☐ Varicella
> **111.** 1 ☐ 0 ☐ Other, specify: _____

112. Drugs: 1 ☐ Yes 0 ☐ No 8 ☐ Unknown

> Specify:
> **Yes No**
> **113.** 1 ☐ 0 ☐ Ganciclovir
> **114.** 1 ☐ 0 ☐ Bactrim, Septra, Trimethoprim-sulfamethoxazole
> **115.** 1 ☐ 0 ☐ Other, specify: _____

116. Etiology undetermined: 1 ☐ Yes 0 ☐ No

TEAM [ ][ ][ ]   IUBMID [ ][ ][ ][ ][ ][ ]

Megakaryopoiesis

The following questions relate to __initial__ platelet recovery. All dates should reflect no transfusions in previous 7 days, and the first of 3 consecutive laboratory results.

117. Did recipient achieve an **initial** platelet count of $\geq$20 x 10^9/L <u>since last report</u>?

   1 ❑ Yes———(Go to Q.118)

   2 ❑ No, recipient achieved a platelet count of $\geq$20 x 10^9/L but <50 x 10^9/L <u>prior</u> to last report———(Go to Q.119)

   3 ❑ No, recipient achieved a platelet count of $\geq$50 x 10^9/L but <100 x 10^9/L <u>prior</u> to last report———(Go to Q.121)

   4 ❑ No, recipient achieved a platelet count of $\geq$100 x 10^9/L <u>prior</u> to last report———(Go to Q.125)

   0 ❑ No, recipient never achieved a platelet count of $\geq$20 x 10^9/L———(Go to Q.123)

118. Date platelets $\geq$20 x 10^9/L: [ ][ ] [ ][ ] [ ][ ] ❑ Date unknown
                             Month Day Year

119. Was a platelet count of $\geq$50 x 10^9/L achieved?

   1 ❑ Yes————— **120.** Date platelets $\geq$50 x 10^9/L: [ ][ ] [ ][ ] [ ][ ] ❑ Date unknown
                                                 Month Day Year

   0 ❑ No—(Go to Q.123)

   8 ❑ Unknown———(Go to Q.123)

121. Was a platelet count of $\geq$100 x 10^9/L achieved?

   1 ❑ Yes————— **122.** Date platelets $\geq$100 x 10^9/L: [ ][ ] [ ][ ] [ ][ ] ❑ Date unknown
                                               Month Day Year

   0 ❑ No

   8 ❑ Unknown

123. Was recipient ever platelet transfusion independent?

   1 ❑ Yes—————

   0 ❑ No——(Go to Q.125 if platelet count of $\geq$20 x 10^9/L achieved; otherwise go to Q.133)

124. Date of the last platelet transfusion*:

❑ Reported on last report [ ][ ] [ ][ ] [ ][ ] ❑ Date unknown
                                      Month Day Year

*If recipient was platelet transfusion independent for $\geq$14 days but subsequently experienced a decline in platelet count and required platelet transfusions, record date of last platelet transfusion <u>before decline in counts</u>. If recipient has not required platelet transfusions since initial platelet recovery record date of last platelet transfusion.

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125. After initial recovery to platelet count $\geq 20 \times 10^9$/L did the platelet count decline to $<20 \times 10^9$/L for 3 consecutive laboratory values or decline to $<20 \times 10^9$/L for one laboratory value and the recipient received a platelet transfusion?

1 ☐ Yes

0 ☐ No

> Go to **Q.159** if platelet count of $\geq 100 \times 10^9$/L achieved; otherwise go to **Q.133**

126. Date of the first day that platelet count declined below 20×10^9/L:

☐☐ ☐☐ ☐☐
Month Day Year

☐ Date unknown

127. Has platelet count recovered?   1 ☐ Yes   0 ☐ No —— Go to **Q.133**

The following date questions relate to **subsequent** platelet recovery following a decline of platelet count to below 20×10^9/L. All dates should reflect no transfusions in previous 7 days, and the first of 3 consecutive laboratory values.

128. Was a platelet count of $\geq 20 \times 10^9$/L achieved?   1 ☐ Yes   0 ☐ No —— Go to **Q.131**

129. Was a platelet count of $\geq 50 \times 10^9$/L achieved?   1 ☐ Yes   0 ☐ No —— Go to **Q.131**

130. Was a platelet count of $\geq 100 \times 10^9$/L achieved?   1 ☐ Yes   0 ☐ No

131. Was patient ever transfusion independent following recovery from decline?   1 ☐ Yes   0 ☐ No

132. Date of the last platelet transfusion (following recovery from decline):

☐☐ ☐☐ ☐☐
Month Day Year

☐ Date unknown

Suspected etiology of failure to achieve a platelet count ≥100 x 10^9/L or decline in platelet count to <20 x 10^9/L:

133. Persistent disease or relapse: 1 ☐ Yes 0 ☐ No 8 ☐ Unknown

134. Graft versus host disease: 1 ☐ Yes 0 ☐ No 8 ☐ Unknown

135. Non-viral infection: 1 ☐ Yes 0 ☐ No 8 ☐ Unknown

136. Immune-mediated: 1 ☐ Yes 0 ☐ No 8 ☐ Unknown
(includes graft rejection)

Immune mediated etiology:

	Yes	No	
137.	1 ☐	0 ☐	Cellular
138.	1 ☐	0 ☐	Antibody
139.	1 ☐	0 ☐	Third party engraftment
140.	1 ☐	0 ☐	Unknown

141. Suspected viral infection: 1 ☐ Yes 0 ☐ No 8 ☐ Unknown

Virus involved:

	Yes	No	
142.	1 ☐	0 ☐	Cytomegalovirus (CMV)
143.	1 ☐	0 ☐	Human Herpes Virus Type 6 (HHV6)
144.	1 ☐	0 ☐	Herpes Simplex Virus (HSV)
145.	1 ☐	0 ☐	Varicella
146.	1 ☐	0 ☐	Other, specify: _____

147. Documented viral infection: 1 ☐ Yes 0 ☐ No 8 ☐ Unknown

Virus involved:

	Yes	No	
148.	1 ☐	0 ☐	Cytomegalovirus (CMV)
149.	1 ☐	0 ☐	Human Herpes Virus Type 6 (HHV6)
150.	1 ☐	0 ☐	Herpes Simplex Virus (HSV)
151.	1 ☐	0 ☐	Varicella
152.	1 ☐	0 ☐	Other, specify: _____

153. Drugs: 1 ☐ Yes 0 ☐ No 8 ☐ Unknown

Therapy:

	Yes	No	
154.	1 ☐	0 ☐	Ganciclovir
155.	1 ☐	0 ☐	Bactrim, Septra, Trimethoprim-sulfamethoxazole
156.	1 ☐	0 ☐	Other, specify: _____

157. Veno-occlusive disease (VOD): 1 ☐ Yes 0 ☐ No 8 ☐ Unknown

158. Etiology undetermined: 1 ☐ Yes 0 ☐ No 2 ☐ Autologous recovery

158.² Other etiology: 1 ☐ Yes 0 ☐ No If yes, specify: _____

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Erythropoiesis

159. Has patient received red blood cell (RBC) transfusions <u>since last report</u>?

   1 ☐ Yes

   0 ☐ No

| **160.** Date of last RBC transfusion:* ☐☐ ☐☐ ☐☐   ☐ Date unknown |
| Month   Day   Year |
| *If patient was RBC transfusion independent for ≥1 month but subsequently experienced a decline in RBC count and required RBC transfusions, record date of last RBC transfusion <u>before decline in counts</u>. If patient has not required RBC transfusions since initial date of recovery, record date of last RBC transfusion. |

Current Hematologic Findings

161. Date of most recent CBC: ☐☐ ☐☐ ☐☐
                          Month Day Year

Actual CBC results

			Specify Units	**Transfused**	**Not Tested**
162.	WBC:	☐☐☐☐☐.☐	1 ☐ x10⁹/L 2 ☐ x10⁶/L		☐
163.	Neutrophils:	☐☐ %			☐
164.	Lymphocytes:	☐☐ %			☐
165.	Hemoglobin:	☐☐☐.☐☐	1 ☐ g/dL 2 ☐ g/L 3 ☐ mmol/L	☐	☐
166.	Hematocrit:	☐☐ %		☐	☐
167.	Platelets:	☐☐☐☐☐	1 ☐ x10⁹/L 2 ☐ x10⁶/L	☐	☐

Actual CBC results columns: WBC uses $\times10^{9}/L$ or $\times10^{6}/L$; Hemoglobin uses g/dL, g/L, or mmol/L; Platelets use $\times10^{9}/L$ or $\times10^{6}/L$.

168. Were chimerism studies performed since last report?

   1 ☐ Yes——(*Complete following page*)

   0 ☐ No——(*Go to Q.169*)

Chimerism Studies

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(Provide date(s), method(s) and other information for all chimerism studies performed since date of last report.)

Date			Method (See Valid List Below)	Cell Type (See Valid List Below)	Number of Cells Examined (Total Cells)	Number of Donor Cells	Number of Host Cells	Number of Unknown Origin (third party) Cells	Percent Donor Cells		Percent Host Cells		Percent Unknown Origin (third party) Cells	
Month	Day	Year							Quantity	*Non-Qty	Quantity	*Non-Qty	Quantity	*Non-Qty

(Grid of data entry boxes)

Valid Method Codes
(Insert number in box above to indicate method used)
1 – Standard Cytogenetics
2 – Fluorescent In situ Hybridization (FISH)
3 – Restriction Fragment-length polymorphisms (RFLP)
4 – Polymerase Chain Reaction (PCR)
5 – HLA typing
6 – VNTR (variable nucleotide tandem repeats) or STR (short tandem repeats)
8 – ABO Blood Group change
90 – Other, specify,_____

Valid Cell Types
(Insert number in box above to indicate cell type used)
1 – Bone Marrow (BM)
2 – Peripheral Blood Mononuclear Cells (PBMC)
3 – T-Cells
4 – B-Cells
5 – Red Cells
6 – Monocytes
7 – Neutrophils
90 – Other, specify,_____

* If performed by non-quantitative method, indicate the presence of donor, host or third party cells by (+)

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Graft-vs-Host Disease (GVHD)

169. Was specific therapy used since last report to prevent <u>or induce</u> GVHD, or promote engraftment?

1 ☐ Yes

0 ☐ No

8 ☐ Unknown

Allografts:
Go to Q.186

Autografts:
Go to Q.326

For each agent listed below indicate whether or not it was used to prevent or induce GVHD since last report:

	Yes	No	
170.	1 ☐	0 ☐	Methotrexate
171.	1 ☐	0 ☐	Cyclosporine
172.	1 ☐	0 ☐	FK 506 (Tacrolimus)
173.	1 ☐	0 ☐	Corticosteroids
174.	1 ☐	0 ☐	ALS, ALG, ATS, ATG
175.	1 ☐	0 ☐	Azathioprine
176.	1 ☐	0 ☐	Cyclophosphamide
177.	1 ☐	0 ☐	In vivo anti T-lymphocyte monoclonal antibody:

Specify:

	Yes	No	
178.	1 ☐	0 ☐	Anti IL-2
179.	1 ☐	0 ☐	Anti CD 25
180.	1 ☐	0 ☐	Campath
181.	1 ☐	0 ☐	OKT3
182.	1 ☐	0 ☐	Other, specify: _____

183. 1 ☐ 0 ☐ In vivo immunotoxin, specify:

_____

184. 1 ☐ 0 ☐ Blinded randomized trial; specify agent being studied: _____

185. 1 ☐ 0 ☐ Other, specify: _____

186. Was acute GVHD present at time of last report?

1 ☐ Yes —— (Go to Q.195)

0 ☐ No

187. Did acute GVHD develop since date of last report?

1 ☐ Yes

0 ☐ No

8 ☐ Unknown

(Go to Q.238)

188. Date of onset: ☐☐ ☐☐ ☐☐
    Month   Day   Year

What was diagnosis based on?

189. Histologic evidence: _____

    1 ☐ Yes

    0 ☐ No

Specify sites:

	Yes	No	
190.	1 ☐	0 ☐	Skin
191.	1 ☐	0 ☐	Gut
192.	1 ☐	0 ☐	Liver
193.	1 ☐	0 ☐	Other, specify: _____

194. Clinical evidence:

    1 ☐ Yes

    0 ☐ No

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195. Maximum overall grade since last report: 1 ☐ I 2 ☐ II 3 ☐ III 4 ☐ IV

List the maximum severity of organ involvement attributed to acute GVHD:

	Stage 0	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**
196. Skin:	1 ☐ No rash	2 ☐ Maculopapular rash, <25% of body surface	3 ☐ Maculopapular rash, 25-50% of body surface	4 ☐ Generalized erythroderma	5 ☐ Generalized erythroderma with bullae formation and desquamation

197. Intestinal tract (use ml/day for adult patients and ml/m²/day for pediatric patients):

0 ☐ No diarrhea	2 ☐ Diarrhea >500 but	3 ☐ Diarrhea >1000 but	4 ☐ Diarrhea	5 ☐ Severe abdominal
1 ☐ Diarrhea ≤500 ml/day or ≤280 ml/m²/day	≤1000 ml/day or 280-555 ml/m²/day	≤1500 ml/day or 556-833 ml/m²/day	>1500 ml/day or >833 ml/m²/day	pain, with or without ileus

198. Liver:

1 ☐ Bilirubin <2.0 mg/dL or <35 µmol/L	2 ☐ Bilirubin 2.0-3.0 mg/dL or 35-52 µmol/L	3 ☐ Bilirubin 3.1-6.0 mg/dL or 53-103 µmol/L	4 ☐ Bilirubin 6.1-15.0 mg/dL or 104-256 µmol/L	5 ☐ Bilirubin >15.0 mg/dL or >256 µmol/L

199. Other organ involvement?

1 ☐ Yes
0 ☐ No

Specify:

       Yes **No**
200. 1 ☐ 0 ☐ Upper GI tract
201. 1 ☐ 0 ☐ Lung
202. 1 ☐ 0 ☐ Other, specify: _____

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203. Was specific therapy used to <u>treat</u> acute GVHD since last report?   1 ☐ Yes   0 ☐ No

For each agent listed below indicate whether or not it was used to <u>treat</u> acute GVHD:

		No, drug not given	Drug continued at prophylactic dose	Yes, drug started or continued for treatment	Yes, dose increased for treatment		Still taking? Yes	No
204.	Methotrexate	0 ☐	1 ☐	2 ☐	3 ☐	**205.**	1 ☐	0 ☐
206.	Cyclosporine	0 ☐	1 ☐	2 ☐	3 ☐	**207.**	1 ☐	0 ☐
208.	FK 506 (Tacrolimus)	0 ☐	1 ☐	2 ☐	3 ☐	**209.**	1 ☐	0 ☐
210.	Systemic Corticosteroids	0 ☐	1 ☐	2 ☐	3 ☐	**211.**	1 ☐	0 ☐
212.	Topical Corticosteroids	0 ☐	1 ☐	2 ☐	3 ☐	**213.**	1 ☐	0 ☐
214.	ALS, ALG, ATS, ATG	0 ☐	1 ☐	2 ☐	3 ☐	**215.**	1 ☐	0 ☐
216.	Azathioprine	0 ☐	1 ☐	2 ☐	3 ☐	**217.**	1 ☐	0 ☐
218.	Cyclophosphamide	0 ☐	1 ☐	2 ☐	3 ☐	**219.**	1 ☐	0 ☐
220.	Thalidomide	0 ☐	1 ☐	2 ☐	3 ☐	**221.**	1 ☐	0 ☐

In vivo anti-T-lymphocyte monoclonal antibody:

		No, drug not given	Drug continued at prophylactic dose	Yes, drug started or continued for treatment	Yes, dose increased for treatment		Still taking? Yes	No
222.	Anti IL-2	0 ☐	1 ☐	2 ☐	3 ☐	**223.**	1 ☐	0 ☐
224.	Anti CD 25	0 ☐	1 ☐	2 ☐	3 ☐	**225.**	1 ☐	0 ☐
226.	Campath	0 ☐	1 ☐	2 ☐	3 ☐	**227.**	1 ☐	0 ☐
228.	OKT3	0 ☐	1 ☐	2 ☐	3 ☐	**229.**	1 ☐	0 ☐
230.	Other antibody,	0 ☐	1 ☐	2 ☐	3 ☐	**231.**	1 ☐	0 ☐

specify:_____

232.	In vivo immunotoxin,	0 ☐	1 ☐	2 ☐	3 ☐	**233.**	1 ☐	0 ☐

specify:_____

234.	Blinded randomized trial;	0 ☐	1 ☐	2 ☐	3 ☐	**235.**	1 ☐	0 ☐

specify agent being studied:_____

236.	Other,	0 ☐	1 ☐	2 ☐	3 ☐	**237.**	1 ☐	0 ☐

specify:_____

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238. Was chronic GVHD present at time of last report?

1 ☐ Yes ── **239.** Chronic GVHD is still present or was present at time of death:

0 ☐ No

    1 ☐ Yes ── Go to Q.256

    0 ☐ No

240. Did clinical chronic GVHD develop since date of last report?

1 ☐ Yes

0 ☐ No ── Go to Q.326

8 ☐ Unknown

241. Date of onset: ☐☐ ☐☐ ☐☐ ── **242.** Progressed from acute GVHD? 1☐ Yes 0☐ No
    Month Day Year

243. Karnofsky/Lansky score (*see page 1*) at diagnosis of chronic GVHD: ☐☐☐

244. Platelet count at diagnosis of chronic GVHD: ☐☐☐☐☐☐☐.☐ 1☐ x10⁹/L 2☐ x10⁹/L

245. Total serum bilirubin at diagnosis of chronic GVHD: ☐☐☐.☐ 1☐ mg/dL 2☐ μmol/L

What was diagnosis based on?
246. Histologic evidence:

1 ☐ Yes

0 ☐ No

255. Clinical evidence:

1 ☐ Yes

0 ☐ No

Specity sites:

    Yes No

247. 1 ☐ 0 ☐ Skin

248. 1 ☐ 0 ☐ Gut

249. 1 ☐ 0 ☐ Liver

250. 1 ☐ 0 ☐ Buccal mucosa/lip

251. 1 ☐ 0 ☐ Conjunctiva

252. 1 ☐ 0 ☐ Lung

253. 1 ☐ 0 ☐ Muscle

254. 1 ☐ 0 ☐ Other, specify: _____

256. Maximum grade of chronic GVHD:

1 ☐ Limited (*Localized skin involvement and/or hepatic dysfunction due to chronic GVHD*)

2 ☐ Extensive (*Generalized skin involvement; or localized skin involvement and/or hepatic dysfunction due to chronic GVHD, plus :*
    -Liver histology showing chronic aggressive hepatitis, bridging necrosis or cirrhosis; or,
    -Involvement of eye: Schirmer's test with < 5 mm wetting; or,
    -Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy; or,
    -Involvement of any other target organ)

257. Overall severity: 1 ☐ Mild 2 ☐ Moderate 3 ☐ Severe

Continued on next page

Continued from previous page

Indicate organ involvement with chronic GVHD from list below:

		Absent	Mild	Moderate	Severe	Present, but unknown Severity	Unknown whether Involved	
Skin/Hair:	258.	0☐	3☐	4☐	5☐	6☐	8☐	Subclinical (biopsy findings only)
	259.	0☐	3☐	4☐	5☐	6☐	8☐	Rash
	260.	0☐	3☐	4☐	5☐	6☐	8☐	Scleroderma
	261.	0☐	3☐	4☐	5☐	6☐	8☐	Dyspigmentation
	262.	0☐	3☐	4☐	5☐	6☐	8☐	Contractures
	263.	0☐	3☐	4☐	5☐	6☐	8☐	Alopecia
	264.	0☐	3☐	4☐	5☐	6☐	8☐	Other skin/hair involvement, specify:
Eyes:	265.	0☐	3☐	4☐	5☐	6☐	8☐	Dry eyes
	266.	0☐	3☐	4☐	5☐	6☐	8☐	Corneal erosion/conjunctivitis
	267.	0☐	3☐	4☐	5☐	6☐	8☐	Other eye involvement, specify:
Mouth:	268.	0☐	3☐	4☐	5☐	6☐	8☐	Lichenoid changes
	269.	0☐	3☐	4☐	5☐	6☐	8☐	Mucositis/ulcers
	270.	0☐	3☐	4☐	5☐	6☐	8☐	Other mouth involvement, specify:
Lung:	271.	0☐	3☐	4☐	5☐	6☐	8☐	Bronchiolitis obliterans
	272.	0☐	3☐	4☐	5☐	6☐	8☐	Other lung involvement, specify:
GI Tract:	273.	0☐	3☐	4☐	5☐	6☐	8☐	Esophageal involvement
	274.	0☐	3☐	4☐	5☐	6☐	8☐	Chronic nausea/vomiting
	275.	0☐	3☐	4☐	5☐	6☐	8☐	Chronic diarrhea
	276.	0☐	3☐	4☐	5☐	6☐	8☐	Malabsorption
	277.	0☐	3☐	4☐	5☐	6☐	8☐	Other GI tract involvement, specify:
Liver:	278.	0☐	3☐	4☐	5☐	6☐	8☐	Liver involvement, specify:
GU Tract:	279.	0☐	3☐	4☐	5☐	6☐	8☐	Vaginitis/stricture
	280.	0☐	3☐	4☐	5☐	6☐	8☐	Other GU involvement, specify:
Musculoskeletal:	281.	0☐	3☐	4☐	5☐	6☐	8☐	Arthritis
	282.	0☐	3☐	4☐	5☐	6☐	8☐	Myositis
	283.	0☐	3☐	4☐	5☐	6☐	8☐	Myasthenia
	284.	0☐	3☐	4☐	5☐	6☐	8☐	Other musculoskeletal involvement, specify:
Hematologic:	285.	0☐	3☐	4☐	5☐	6☐	8☐	Thrombocytopenia
	286.	0☐	3☐	4☐	5☐	6☐	8☐	Eosinophilia
	287.	0☐	3☐	4☐	5☐	6☐	8☐	Autoantibodies
	288.	0☐	3☐	4☐	5☐	6☐	8☐	Other hematologic involvement, specify:
Other:	289.	0☐	3☐	4☐	5☐	6☐	8☐	Specify: _____

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290. Was specific therapy used to <u>treat</u> chronic GVHD since last report?   1 ☐ Yes   0 ☐ No— Go to Q.325

For each agent listed below indicate whether or not it was used to <u>treat</u> chronic GVHD:

		No, drug not given	Drug continued at prophylactic dose	Yes, drug started or continued for treatment	Yes, dose increased for treatment		Still taking? Yes No
291.	ALS, ALG, ATS, ATG	0 ☐	1 ☐	2 ☐	3 ☐	**292.**	1 ☐ 0 ☐
293.	Azathioprine	0 ☐	1 ☐	2 ☐	3 ☐	**294.**	1 ☐ 0 ☐
295.	Cyclosporine	0 ☐	1 ☐	2 ☐	3 ☐	**296.**	1 ☐ 0 ☐
297.	FK 506 (Tacrolimus)	0 ☐	1 ☐	2 ☐	3 ☐	**298.**	1 ☐ 0 ☐
299.	Systemic Corticosteroids	0 ☐	1 ☐	2 ☐	3 ☐	**300.**	1 ☐ 0 ☐
301.	Topical Corticosteroids	0 ☐	1 ☐	2 ☐	3 ☐	**302.**	1 ☐ 0 ☐
303.	Cyclophosphamide	0 ☐	1 ☐	2 ☐	3 ☐	**304.**	1 ☐ 0 ☐
305.	Thalidomide	0 ☐	1 ☐	2 ☐	3 ☐	**306.**	1 ☐ 0 ☐

In vivo anti-T-lymphocyte monoclonal antibody:

307.	Anti IL-2	0 ☐	1 ☐	2 ☐	3 ☐	**308.**	1 ☐ 0 ☐
309.	Anti CD 25	0 ☐	1 ☐	2 ☐	3 ☐	**310.**	1 ☐ 0 ☐
311.	Campath	0 ☐	1 ☐	2 ☐	3 ☐	**312.**	1 ☐ 0 ☐
313.	OKT3	0 ☐	1 ☐	2 ☐	3 ☐	**314.**	1 ☐ 0 ☐
315.	Other antibody,	0 ☐	1 ☐	2 ☐	3 ☐	**316.**	1 ☐ 0 ☐

specify:_____

317.	In vivo immunotoxin,	0 ☐	1 ☐	2 ☐	3 ☐	**318.**	1 ☐ 0 ☐

specify:_____

319.	Blinded randomized trial;	0 ☐	1 ☐	2 ☐	3 ☐	**320.**	1 ☐ 0 ☐

specify agent being studied:_____

321.	Other,	0 ☐	1 ☐	2 ☐	3 ☐	**322.**	1 ☐ 0 ☐

specify:_____

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323. Is patient still receiving treatment for chronic GVHD?

    ₁ ☐ Yes

    ₀ ☐ No——— | **324.** Date last treatment was administered: ☐☐ ☐☐ ☐☐
                                                                        Month Day Year

325. Is chronic GVHD still present?

    ₁ ☐ Yes

    ₀ ☐ No

    ₈ ☐ No symptoms, but patient still receiving treatment

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326. Did patient develop clinically significant infection <u>since date of last report</u>?   1☐ Yes   0☐ No

Select site and organism from lists shown on the next page and place number in the appropriate spaces. If more than one site or organism was involved, list one site of infection and organism on the first line; second site and/or organism on second line.

		Site	**Organism**	**Date of Onset** **Month Day Year**	**Did infection resolve?** **Yes No**
327. ☐ Bacterial					
<u>Typical</u> First	**328.** ☐☐	**329.** _____	**330.** ☐☐☐☐☐☐	**331.** 1☐ 0☐
Second	**332.** ☐☐	**333.** _____	**334.** ☐☐☐☐☐☐	**335.** 1☐ 0☐
<u>Atypical</u> First	**337.** ☐☐	**338.** B☐☐☐	**339.** ☐☐☐☐☐☐	**340.** 1☐ 0☐
Second	**341.** ☐☐	**342.** B☐☐☐	**343.** ☐☐☐☐☐☐	**344.** 1☐ 0☐

345. Other atypical bacterium, specify: _____

346. ☐ Fungal

First	**347.** ☐☐	**348.** F☐☐☐	**349.** ☐☐☐☐☐☐	**350.** 1☐ 0☐
Second	**351.** ☐☐	**352.** F☐☐☐	**353.** ☐☐☐☐☐☐	**354.** 1☐ 0☐

355. Other fungus, specify: _____

356. ☐ Viral

First	**357.** ☐☐	**358.** V☐☐☐	**359.** ☐☐☐☐☐☐	**360.** 1☐ 0☐
Second	**361.** ☐☐	**362.** V☐☐☐	**363.** ☐☐☐☐☐☐	**364.** 1☐ 0☐

365. Other virus, specify: _____

366. ☐ Parasitic

First	**367.** ☐☐	**368.** P☐☐☐	**369.** ☐☐☐☐☐☐	**370.** 1☐ 0☐
Second	**371.** ☐☐	**372.** P☐☐☐	**373.** ☐☐☐☐☐☐	**374.** 1☐ 0☐

375. Other parasite, specify: _____

376. ☐ No organism identified

First	**377.** ☐☐	**378.** O☐☐☐	**379.** ☐☐☐☐☐☐	**380.** 1☐ 0☐
Second	**381.** ☐☐	**382.** O☐☐☐	**383.** ☐☐☐☐☐☐	**384.** 1☐ 0☐

Codes for Common Sites of Infection

1 Blood/buffy coat
2 Disseminated – generalized, isolated at 3 or more distinct sites
3 *Central Nervous System unspecified*
4 Brain
5 Spinal cord
6 Meninges and CSF
10 *Gastrointestinal Tract unspecified*
11 Lips
12 Tongue, oral cavity and oro-pharynx
13 Esophagus
14 Stomach
15 Gallbladder and biliary tree (not hepatitis), pancreas
16 Small intestine
17 Large intestine
18 Feces/stool
19 Peritoneum
20 Liver
30 *Respiratory unspecified*
31 Upper airway and nasopharynx
32 Laryngitis/larynx
33 Lower respiratory tract (lung)
34 Pleural cavity, pleural fluid
35 Sinuses

40 *Genito-Urinary Tract unspecified*
41 Kidneys, renal pelvis, ureters and bladder
42 Prostate
43 Testes
44 Fallopian tubes, uterus, cervix
45 Vagina
50 *Skin unspecified*
51 Genital area
52 Cellulitis
53 Herpes Zoster
54 Rash, pustules or abscesses not typical of any of the above
60 *Central venous catheter unspecified*
61 Catheter insertion or exit site
62 Catheter tip
70 Eyes
75 Ear
81 Joints
82 Bone marrow
83 Bone cortex (osteomyelitis)
84 Muscle (excluding cardiac)
85 Cardiac (endocardium, myocardium, pericardium)
86 Lymph nodes
87 Spleen

Codes for Commonly Reported Organisms

1. Bacteria (Indicate code for atypical bacteria; list bacterium for non-atypical bacteria in **Q.329, 330.**)

100 Atypical bacteria, not otherwise specified
101 Coxiella
102 Legionella
103 Leptospira
104 Listeria
105 Mycoplasma
106 Nocardia
107 Rickettsia
110 Tuberculosis, NOS (AFB, acid fast bacillus, Koch bacillus)
111 Typical tuberculosis (TB, Tuberculosis)
112 Mycobacteria (avium, bovium, intracellulare)
113 Chlamydia
119 Other atypical bacteria, *specify in Q.345*

2. Fungal Infections
200 Candida, not otherwise specified
201 Candida albicans
202 Candida krusei
203 Candida parapsilosis
204 Candida tropicalis
205 Torulopsis glabrata (a subspecies of candida)
209 Other Candida, *specify in Q.355*
210 Aspergillus, not otherwise specified
211 Aspergillus flavus
212 Aspergillus fumigatus
213 Aspergillus niger
219 Other Aspergillus, *specify in Q.355*
220 Cryptococcus species
230 Fusarium species
240 Mucormycosis (zygomycetes, rhizopus)
250 Yeast, not otherwise specified
259 Other fungus, *specify in Q.355*

3. Viral Infections
301 Herpes Simplex (HSV1, HSV2)
302 Herpes Zoster (Chicken pox, Varicella)
303 Cytomegalovirus (CMV)
304 Adenovirus
305 Enterovirus (Coxsackie, Echo, Polio)
306 Hepatitis A (HAV)
307 Hepatitis B (HBV, Australian antigen)
308 Hepatitis C (HCV)
309 HIV-1 (HTLV-III)
310 Influenza
311 Measles (Rubeola)
312 Mumps
313 Papovavirus
314 Respiratory syncytial virus (RSV)
315 Rubella (German Measles)
316 Parainfluenza
317 Human herpesvirus-6 (HHV-6)
318 Epstein-Barr virus (EBV)
319 Polyomavirus
320 Rotavirus
321 Rhinovirus
329 Other viral, *specify in Q.365*

4. Parasite Infections
401 Pneumocystis (PCP)
402 Toxoplasma
403 Giardia
404 Cryptosporidium
409 Other parasite (amebiasis, echinococcal cyst, trichomonas – either vaginal or gingivitis), *specify in Q.375*

5. Other Infections
501 Suspected atypical bacterial infection
502 Suspected bacterial infection
503 Suspected fungal infection
504 Suspected viral infection
505 Suspected parasite infection
509 No organism identified

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Pulmonary function

385. Has patient developed interstitial pneumonitis (IPn) since date of last report?

> *Interstitial pneumonitis is characterized by hypoxia and diffuse interstitial infiltrates on chest x-ray not caused by fluid overload.*

1 ☐ Yes
0 ☐ No

386. How many episodes of IPn occurred since date of last report? ☐

> *Note: If more than one episode of IPn, photocopy this page and complete Q.387-406 for subsequent episode(s).*

387. Date of onset of IPn: ☐☐ ☐☐ ☐☐
Month Day Year

388. Were diagnostic tests other than radiographic studies done?

1 ☐ Yes
0 ☐ No

Diagnosis was evaluated by:

	Yes	**No**	
389.	1 ☐	0 ☐	Bronchoalveolar lavage
390.	1 ☐	0 ☐	Transbronchial biopsy
391.	1 ☐	0 ☐	Open lung biopsy
392.	1 ☐	0 ☐	Autopsy
393.	1 ☐	0 ☐	Other, specify: _____

394. Was an organism isolated?

1 ☐ Yes
0 ☐ No (idiopathic, or no organism isolated)

Etiology:

	Yes	**No**	
395.	1 ☐	0 ☐	Pneumocystis carinii
396.	1 ☐	0 ☐	Aspergillus
397.	1 ☐	0 ☐	Candida
398.	1 ☐	0 ☐	Toxoplasma
399.	1 ☐	0 ☐	Respiratory syncytial virus
400.	1 ☐	0 ☐	Cytomegalovirus
401.	1 ☐	0 ☐	Herpes simplex
402.	1 ☐	0 ☐	Adenovirus
403.	1 ☐	0 ☐	Human herpes virus 6
404.	1 ☐	0 ☐	Other virus, specify:_____
405.	1 ☐	0 ☐	Other, specify: _____

406. Has interstitial pneumonitis resolved?

1 ☐ Yes
0 ☐ No
8 ☐ Unknown

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407. Did patient develop pulmonary abnormalities other than interstitial pneumonitis since date of last report?

1 ☐ Yes

0 ☐ No

408. Did patient develop Acute Respiratory Distress Syndrome (ARDS) since last report?

1 ☐ Yes

0 ☐ No

409. Date of onset of ARDS: ☐☐ ☐☐ ☐☐
Month Day Year

410. Were diagnostic tests done?

1 ☐ Yes

0 ☐ No

Diagnosis was evaluated by:

    Yes **No**

411. 1 ☐ 0 ☐ Bronchoalveolar lavage

412. 1 ☐ 0 ☐ Transbronchial biopsy

413. 1 ☐ 0 ☐ Open lung biopsy

414. 1 ☐ 0 ☐ Autopsy

415. 1 ☐ 0 ☐ Other, specify: _____

416. Did patient develop bronchiolitis obliterans since last report?

1 ☐ Yes

0 ☐ No

417. Date of onset: ☐☐ ☐☐ ☐☐
Month Day Year

418. Were diagnostic tests done?

1 ☐ Yes

0 ☐ No

Diagnosis was evaluated by:

    Yes **No**

419. 1 ☐ 0 ☐ Bronchoalveolar lavage

420. 1 ☐ 0 ☐ Transbronchial biopsy

421. 1 ☐ 0 ☐ Open lung biopsy

422. 1 ☐ 0 ☐ Autopsy

423. 1 ☐ 0 ☐ Other, specify: _____

424. Did patient develop pulmonary hemorrhage since last report?

1 ☐ Yes

0 ☐ No

425. Date of onset: ☐☐ ☐☐ ☐☐
Month Day Year

426. Were diagnostic tests done?

1 ☐ Yes

0 ☐ No

Diagnosis was evaluated by:

    Yes **No**

427. 1 ☐ 0 ☐ Bronchoalveolar lavage

428. 1 ☐ 0 ☐ Transbronchial biopsy

429. 1 ☐ 0 ☐ Open lung biopsy

430. 1 ☐ 0 ☐ Autopsy

431. 1 ☐ 0 ☐ Other, specify: _____

432. Did patient develop other non-infectious pulmonary abnormalities since last report?

1 ☐ Yes

0 ☐ No

433. Specify: _____

TEAM [ ][ ][ ][ ]   IUBMID [ ][ ][ ][ ][ ][ ]

Liver function

434. Did patient develop non-infectious liver toxicity since last report?

1 ☐ Yes

0 ☐ No

> 435. What was the date of onset? [ ][ ] [ ][ ] [ ][ ]
> Month Day Year
>
> Etiology:
>
> Yes No
> 436. 1 ☐ 0 ☐ Veno-occlusive disease
> 437. 1 ☐ 0 ☐ Other, specify: _____
> 438. 1 ☐ 0 ☐ Unknown
>
> 439. Has liver toxicity resolved?
> 1 ☐ Yes
> 0 ☐ No
> 8 ☐ Unknown

440. Did patient develop any other non-infectious clinically significant organ impairment or disorder since last report?

1 ☐ Yes

0 ☐ No

> Yes No
> 441. 1 ☐ 0 ☐ Renal failure requiring dialysis——(If yes, received dialysis? 1 ☐ Yes 0 ☐ No)
> 442. 1 ☐ 0 ☐ Posttransplant microangiopathy/thrombotic thrombocytopenic purpura (TTP)/ hemolytic uremic syndrome (HUS) or similar syndrome
> 443. 1 ☐ 0 ☐ Hemorrhage, if yes specify site——
> 448. 1 ☐ 0 ☐ Hemorrhagic cystitis
> 449. 1 ☐ 0 ☐ Seizures
> 450. 1 ☐ 0 ☐ Cataracts
> 451. 1 ☐ 0 ☐ Avascular necrosis
> 452. 1 ☐ 0 ☐ Hypothyroidism
> 453. 1 ☐ 0 ☐ Gonadal dysfunction
> 454. 1 ☐ 0 ☐ Growth hormone deficiency/growth disturbance
> 455. 1 ☐ 0 ☐ Other, specify: _____
>
> > Yes No
> > 444. 1 ☐ 0 ☐ CNS
> > 445. 1 ☐ 0 ☐ Upper GI tract
> > 446. 1 ☐ 0 ☐ Lower GI tract
> > 447. 1 ☐ 0 ☐ Other, specify:
> > _____

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456. Did a <u>new</u> malignancy, lymphoproliferative or myeloproliferative disorder appear since last report?

1 ☐ Yes

0 ☐ No

456.² Did more than one new malignancy develop?

1 ☐ Yes — *Copy page and answer Q.457-469 for each new malignancy*

0 ☐ No

457. Date of diagnosis: ☐☐ ☐☐ ☐☐
Month Day Year

458. Origin of cells: 1 ☐ Host 2 ☐ Donor 7 ☐ Not tested 8 ☐ Unknown

Diagnosis (*send copy of pathology report/other documentation*):

Yes No

459. 1 ☐ 0 ☐ Clonal cytogenetic abnormality without leukemia or MDS

460. 1 ☐ 0 ☐ Acute myeloid leukemia

461. 1 ☐ 0 ☐ Other leukemia, specify: _____

462. 1 ☐ 0 ☐ Myelodysplasia

463. 1 ☐ 0 ☐ Lymphoma or lymphoproliferative disease

464. EBV positive? 1 ☐ Yes 0 ☐ No 8 ☐ Unknown

465. 1 ☐ 0 ☐ Hodgkin disease

466. 1 ☐ 0 ☐ Other cancer

467. Primary site: _____

468. Histologic type: _____

469. Behavior:

1 ☐ Benign

2 ☐ In situ

3 ☐ Malignant/invasive

8 ☐ Unknown

TEAM ☐☐☐☐   IUBMID ☐☐☐☐☐☐

Death Information

470. Date of death: ☐☐☐☐☐☐
Month   Day   Year

<u>Cause(s) of death:</u>

Enter appropriate cause of death below.	**Cause of Death Codes***
	10 Graft rejection or failure

Enter appropriate cause of death below.

If a code number for "Other, specify" (codes 29, 39, 88, 89, 109, 129, 900) is entered, write the cause in the space provided.

471. Primary: ☐☐☐ Specify: _____

Contributing or secondary causes:

472. ☐☐☐ Specify: _____

473. ☐☐☐ Specify: _____

474. ☐☐☐ Specify: _____

475. ☐☐☐ Specify: _____

476. ☐☐☐ Specify: _____

Cause of Death Codes*

10 Graft rejection or failure

Infection (other than interstitial pneumonia)
- 20 Infection, organism not identified
- 21 Bacterial
- 22 Fungal
- 23 Viral
- 24 Protozoal
- 29 Other infection, specify

Interstitial pneumonia
- 30 IPn, idiopathic
- 31 Cytomegalovirus (CMV)
- 32 Viral, other
- 33 Pneumocystis (PCP)
- 34 Fungal
- 39 Other IPn, specify

40 Adult Respiratory Distress Syndrome, ARDS (other than IPn)

50 Acute GVHD
60 Chronic GVHD

70 Recurrence or persistence of primary disease

    * *NOTE: Code "70" may only be used as a primary cause of death, not a contributing or secondary cause.*

Organ failure (not due to GVHD or infection)
- 80 Organ failure, not otherwise specified
- 81 Liver (not VOD)
- 82 VOD
- 83 Cardiac (Cardiomyopathy)
- 84 Pulmonary
- 85 CNS ·
- 86 Renal
- 87 Gastrointestinal (not liver)
- 88 Multiple organ failure, specify
- 89 Other organ failure, specify

90 Secondary malignancy

(malignancy other than one for which transplant performed includes post transplant lymphoproliferative disease and MDS)

Hemorrhage
- 100 Hemorrhage, not otherwise specified
- 101 Pulmonary
- 102 Intracranial
- 103 Gastrointestinal
- 109 Other hemorrhage, specify

110 Accidental death

Vascular
- 120 Vascular, not otherwise specified
- 121 Thromboembolic
- 122 Diffused intrevascular congulation (DIC)
- 123 Thrombotic thrombocytopenic purpura
- 129 Other vascular, specify

130 In utero death (for in utero transplants)

140 Prior malignancy

(malignancy existing before disease for which transplant performed as reported in 095-COR Form Q.41)

900 Other, specify

477. Was cause of death confirmed by autopsy?

1 ☐ Yes
0 ☐ No
8 ☐ Unknown
6 ☐ Pending

Send copy of autopsy report when available
Autopsy included with this report:
   1 ☐ Yes   0 ☐ No

FOLLOW-UP INSTITUTIONAL INFORMATION

TEAM ☐☐☐☐   IUBMID ☐☐☐☐☐☐
(Institutional Unique Blood or Marrow Transplant Identification Number)

Registry: IBMTR   ABMTR   *(circle one)*

Date of transplant for which
this form is being completed: ☐☐ ☐☐ ☐☐
Month Day Year

Date of report: ☐☐ ☐☐ ☐☐
Month Day Year

1. Signed: _____ / _____
Person completing this form / Please print name

3. Name of doctor for correspondence: _____

   Institution: _____

   Address: _____

   _____

   _____

   Telephone: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐   Ext: ☐☐☐☐☐

   Fax: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

4. Make reimbursement check payable to: _____
   Payment for data forms is contingent on the availability of funds that have been obtained from sources external to the Medical College of Wisconsin for purposes of these payments.

5. Patient or authorized family member/guardian is aware of, and has consented to, the fact that this case is being entered into the Registry database:
   _____(physician's initials).

6. Determining cut-off for all parts of this report:
   A complete follow-up report of transplant consists of the following two parts (both parts should have the same date of report, date of transplant and contact date):
   • A (white) CORE Follow-up form
   • An appropriate (ivory) disease-specific insert (Inserts I through XVIII)

   Report Form = | Follow-up CORE Form | + | Disease Insert |

   The cut-off for **ALL** parts of this Report Form should be the date of the follow-up exam closest to the transplant anniversary date, unless (a)patient died, or (b) patient received a subsequent transplant or infusion >14 days but <100 days post transplant which requires a separate Report Form. (See pages 3 & 4 of the CORE Follow-up Form to determine if the re-infusions is considered another transplant requiring a separate Report Form.)

   The date of Last Contact is the date of the follow-up exam or (a) the date of death, or (b) one day prior to conditioning for subsequent transplant or one day prior to subsequent transplant/infusion if no conditioning given.

   Enter Last Contact date (e.g., Month, Day, Year): ☐☐ ☐☐ ☐☐

   Enter these dates on page 1 of the CORE Follow-up Form. Report information in the CORE Follow-up Form and disease-specific insert only up to Last Contact date. Later information should be reported in the next Follow-up Form or Report Form for a subsequent transplant when it is due.

   If completing Follow-up Form for >2 years of data, report all data on one Follow-up Form.
   Begin completing annual Follow-up Forms thereafter.

TEAM ☐☐☐☐ IUBMID ☐☐☐☐☐☐☐

(Institutional Unique Blood or Marrow Transplant Identification Number)

Date of transplant for which this form is being completed: ☐☐ ☐☐ ☐☐
Month Day Year

Date of report: ☐☐ ☐☐ ☐☐
Month Day Year

Autologous Bone Marrow Collection and Processing

1. Date of bone marrow harvest: ☐☐ ☐☐ ☐☐
Month Day Year

1.2 Did patient receive treatment <u>prior</u> <u>to</u> harvesting to enhance bone marrow collection?

1 ☐ Yes

0 ☐ No

> What treatment did patient receive?
>
> **1.3** Chemotherapy:
>
> 1 ☐ Yes
>
> 0 ☐ No
>
> **1.4** Growth factors:
>
> 1 ☐ Yes
>
> 0 ☐ No
>
> | | Yes | No | |
> |---|---|---|---|
> | **1.5** | 1 ☐ | 0 ☐ | G-CSF |
> | **1.6** | 1 ☐ | 0 ☐ | GM-CSF |
> | **1.7** | 1 ☐ | 0 ☐ | Other, specify: _____ |
>
> **1.8** 1 ☐ Yes 0 ☐ No Other, specify: _____

2. *For leukemia/lymphoma patients only:*

What was disease state at time of harvest?

1 ☐ First remission

2 ☐ Second remission **3.** Date of remission: ☐☐ ☐☐ ☐☐
Month Day Year

3 ☐ Third remission

4 ☐ First relapse

5 ☐ Second relapse

7 ☐ Other, specify: _____

4. Was bone marrow cryopreserved?

1 ☐ Yes ———

0 ☐ No

> **5.** Cryopreservative was:
>
> 1 ☐ DMSO
>
> 2 ☐ Hydroxyethylstarch
>
> 7 ☐ Other, specify: _____

Indicate whether or not tumor involvement of bone marrow or circulating cells was detected <u>prior to transplant</u> by each of the indicated methods:

	Detected in circulating cells*				Detected in bone marrow, prior to harvest*				Detected in harvested bone marrow (before purging)		
	Yes	No	Not Tested		Yes	No	Not Tested		Yes	No	Not Tested
Routine histopathology	**6.** 1☐	0☐	7☐	**7.**	1☐	0☐	7☐	**8.**	1☐	0☐	7☐
Polymerase chain reaction (PCR)	**9.** 1☐	0☐	7☐	**10.**	1☐	0☐	7☐	**11.**	1☐	0☐	7☐
Other molecular technique	**12.** 1☐	0☐	7☐	**13.**	1☐	0☐	7☐	**14.**	1☐	0☐	7☐
Immunohistochemistry	**15.** 1☐	0☐	7☐	**16.**	1☐	0☐	7☐	**17.**	1☐	0☐	7☐
Cell culture technique	**18.** 1☐	0☐	7☐	**19.**	1☐	0☐	7☐	**20.**	1☐	0☐	7☐
Other, specify: _____	**21.** 1☐	0☐	7☐	**22.**	1☐	0☐	7☐	**23.**	1☐	0☐	7☐

* Refers to detection of tumor cells in circulation or bone marrow in the interval between last chemotherapy and harvest.

24. Was bone marrow treated to remove malignant cells (purged)?

1 ☐ Yes ———

0 ☐ No

> Which of the following were used for purging?
>
>   Yes No
>
> **25.** 1☐ 0☐ Monoclonal antibody, specify: _____
>
> **26.** 1☐ 0☐ 4-hydroperoxycyclophosphamide (4HC)
>
> **27.** 1☐ 0☐ Mafosfamide
>
> **28.** 1☐ 0☐ Other drug, specify: _____
>
> **29.** 1☐ 0☐ Elutriation
>
> **30.** 1☐ 0☐ Immunomagnetic column
>
> **31.** 1☐ 0☐ Toxin, specify: _____
>
> **32.** 1☐ 0☐ Positive stem cell selection (other than preparation of mononuclear fraction)
>   Specify method: _____
>
> **33.** 1☐ 0☐ Other, specify: _____
>
> *continued on next page*

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Indicate whether or not tumor involvement of harvested bone marrow was detected <u>after purging</u> by each of the indicated methods:

	Yes	No	Not Tested	
34.	1 ☐	0 ☐	7 ☐	Routine histopathology
35.	1 ☐	0 ☐	7 ☐	Polymerase chain reaction (PCR)
36.	1 ☐	0 ☐	7 ☐	Other molecular technique
37.	1 ☐	0 ☐	7 ☐	Immunohistochemistry
38.	1 ☐	0 ☐	7 ☐	Cell culture technique
39.	1 ☐	0 ☐	7 ☐	Other, specify: _____

40. Were cells (or a portion of cells) expanded <u>ex</u> <u>vivo</u> prior to infusion?

1 ☐ Yes
0 ☐ No

41. Days of expansion culture: ☐☐☐

Growth factors used:

	Yes	No	
42.	1 ☐	0 ☐	G-CSF
43.	1 ☐	0 ☐	GM-CSF
44.	1 ☐	0 ☐	IL-2
45.	1 ☐	0 ☐	IL-3
46.	1 ☐	0 ☐	IL-6
47.	1 ☐	0 ☐	SCF
48.	1 ☐	0 ☐	Thrombopoietin
49.	1 ☐	0 ☐	M-CSF
50.	1 ☐	0 ☐	PIXY 321
51.	1 ☐	0 ☐	Other, specify: _____

52. Number of nucleated cells pre-expansion: ☐☐☐.☐ $\times 10^{10}$

53. Number of nucleated cells post-expansion: ☐☐☐.☐ $\times 10^{10}$

54. Total number of nucleated cells infused: ☐☐☐.☐ $\times 10^{10}$

55. Total number of mononucleated cells infused: ☐☐☐.☐ $\times 10^{10}$

56. Were bone marrow progenitor assays done?

1 ☐ Yes
0 ☐ No

57. Number of CD34+ cells infused: ☐☐☐.☐ $\times 10^{7}$ -8 ☐ Unknown

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(Institutional Unique Blood or Marrow Transplant Identification Number)

Registry: IBMTR   ABMTR   *(circle one)*

Date of transplant for which this form is being completed: ☐☐ ☐☐ ☐☐
Month   Day   Year

Date of report: ☐☐ ☐☐ ☐☐
Month   Day   Year

Autologous Blood Collection and Processing

1. What was the reason for using blood rather than bone marrow for hematopoietic reconstitution?

  1 ☐ All patients receive peripheral blood cells, per protocol
  2 ☐ Bone marrow involvement with tumor
  3 ☐ Prior radiation to pelvis
  4 ☐ Inadequate bone marrow cellularity
  7 ☐ Other, specify: _____

2. Date of first stem cell collection: ☐☐ ☐☐ ☐☐
Month   Day   Year

3. Date of last stem cell collection: ☐☐ ☐☐ ☐☐
Month   Day   Year

4. Number of collections: ☐☐

5. Did patient receive treatment <u>prior to</u> harvesting to enhance stem cell collection?

  1 ☐ Yes
  0 ☐ No

What treatment did patient receive?

6. Chemotherapy:
  1 ☐ Yes
  0 ☐ No

7. Growth factors:
  1 ☐ Yes
  0 ☐ No

	Yes	No	
8.	1 ☐	0 ☐	G-CSF
9.	1 ☐	0 ☐	GM-CSF
10.	1 ☐	0 ☐	Other, specify: _____

11. 1 ☐ Yes 0 ☐ No Other, specify: _____

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12. *For leukemia/lymphoma patients only:*

What was disease state at time of stem cell collections?

1 ☐ First remission ⎯⎯⎯⎯⎯⎯┐

2 ☐ Second remission ⎯ Date of remission: ☐☐ ☐☐ ☐☐
                                        Month Day Year

3 ☐ Third remission ⎯⎯⎯⎯⎯⎯┘

4 ☐ First relapse

5 ☐ Second relapse

7 ☐ Other, specify: _____

13. Were cells cryopreserved?

1 ☐ Yes ⎯⎯⎯ **14.** Cryopreservative was:
0 ☐ No   1 ☐ DMSO
               2 ☐ Hydroxyethylstarch
               7 ☐ Other, specify: _____

Indicate whether or not tumor involvement of bone marrow or circulating cells was detected <u>prior to transplant</u>
by each of the indicated methods:

	Detected in circulating cells*			Detected in bone marrow, prior to harvest*			Detected in harvested cells (before purging)		
	Yes	No	Not Tested	Yes	No	Not Tested	Yes	No	Not Tested
Routine histopathology	**15.** 1☐	0☐	7☐	**16.** 1☐	0☐	7☐	**17.** 1☐	0☐	7☐
Polymerase chain reaction (PCR)	**18.** 1☐	0☐	7☐	**19.** 1☐	0☐	7☐	**20.** 1☐	0☐	7☐
Other molecular technique	**21.** 1☐	0☐	7☐	**22.** 1☐	0☐	7☐	**23.** 1☐	0☐	7☐
Immunohistochemistry	**24.** 1☐	0☐	7☐	**25.** 1☐	0☐	7☐	**26.** 1☐	0☐	7☐
Cell culture technique	**27.** 1☐	0☐	7☐	**28.** 1☐	0☐	7☐	**29.** 1☐	0☐	7☐
Other, specify:	**30.** 1☐	0☐	7☐	**31.** 1☐	0☐	7☐	**32.** 1☐	0☐	7☐

* *Refers to detection of tumor cells in circulation or bone marrow in the interval between last chemotherapy and stem cell collection.*

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33. Were cells treated to remove malignant cells (purged)? 1 ☐ Yes 0 ☐ No

Which of the following were used for purging?

    Yes No

34. 1 ☐ 0 ☐ Monoclonal antibody, specify: _____

35. 1 ☐ 0 ☐ 4-hydroperoxycyclophosphamide (4HC)

36. 1 ☐ 0 ☐ Mafosfamide

37. 1 ☐ 0 ☐ Other drug, specify: _____

38. 1 ☐ 0 ☐ Elutriation

39. 1 ☐ 0 ☐ Immunomagnetic column

40. 1 ☐ 0 ☐ Toxin, specify: _____

41. 1 ☐ 0 ☐ Positive stem cell selection (other than preparation of mononuclear fraction)
               Specify method: _____

42. 1 ☐ 0 ☐ Other, specify: _____

Indicate whether or not tumor cells were detected in the graft <u>after purging</u>
by each of the indicated methods:

    Yes No Not Tested

43. 1 ☐ 0 ☐ 7 ☐   Routine histopathology

44. 1 ☐ 0 ☐ 7 ☐   Polymerase chain reaction (PCR)

45. 1 ☐ 0 ☐ 7 ☐   Other molecular technique

46. 1 ☐ 0 ☐ 7 ☐   Immunohistochemistry

47. 1 ☐ 0 ☐ 7 ☐   Cell culture technique

48. 1 ☐ 0 ☐ 7 ☐   Other, specify: _____

49. Were cells expanded <u>ex vivo</u> prior to infusion?

1 ☐ Yes
0 ☐ No

50. Days of expansion culture: ☐☐☐

Growth factors used:
    Yes No

51. 1 ☐ 0 ☐ G-CSF

52. 1 ☐ 0 ☐ GM-CSF

53. 1 ☐ 0 ☐ IL-2

54. 1 ☐ 0 ☐ IL-3

55. 1 ☐ 0 ☐ IL-6

56. 1 ☐ 0 ☐ SCF

57. 1 ☐ 0 ☐ Thrombopoietin

58. 1 ☐ 0 ☐ M-CSF

59. 1 ☐ 0 ☐ PIXY 321

60. 1 ☐ 0 ☐ Other, specify: _____

61. Number of nucleated cells pre-expansion: ☐☐☐.☐ $\times 10^{10}$

62. Number of nucleated cells post-expansion: ☐☐☐.☐ $\times 10^{10}$

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63. Total number of <u>nucleated</u> cells infused: ☐☐☐.☐ $\times 10^{10}$

64. Total number of <u>mononucleated</u> cells infused: ☐☐☐.☐ $\times 10^{10}$

65. Were progenitor cell assays done?

    1 ☐ Yes

    0 ☐ No

66. Number of CD34+ cells infused: ☐☐☐.☐ $\times 10^{7}$ -8 ☐ Unknown

INSERT VIII
Breast Cancer

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(Institutional Unique Blood or Marrow Transplant Identification Number)

Date of transplant for which this form is being completed: ☐☐ ☐☐ ☐☐
Month Day Year

Registry: IBMTR   ABMTR   (circle one)

Date of report: ☐☐ ☐☐ ☐☐
Month Day Year

Pretransplant Information

* If this is a report of a second (or subsequent) transplant, check here ☐ and go to Q.168

1. Date of pathologic diagnosis of breast cancer: ☐☐ ☐☐
   Month Year
   Append copy of pathology report if available.

   If transplant was done after occurence of a second primary breast cancer, report staging and treatment [Q.1-75] of each primary separately by copying pages 1-4.

2. Stage of breast cancer at diagnosis:

   0 ☐ In situ
   1 ☐ I   - $T_1 N_0 M_0$
   2 ☐ II   - $T_{0,1} N_1 M_0$ or $T_2 N_{0,1} M_0$ or $T_3 N_0 M_0$
   3 ☐ IIIA - $T_{0-2} N_2 M_0$ or $T_3 N_{1-2} M_0$
   4 ☐ IIIB - $T_4 N_{Any} M_0$, $T_{Any} N_3 M_0$, Inflammatory
   5 ☐ IV   - $T_{Any} N_{Any} M_1$
   8 ☐ Unknown

3. Breast cancer histology at diagnosis:

   1 ☐ Invasive/infiltrating ductal
   2 ☐ Invasive lobular
   3 ☐ Inflammatory
   4 ☐ Other, specify: _____
   8 ☐ Unknown

4. Location of breast cancer at diagnosis:

   1 ☐ Right breast
   2 ☐ Left breast
   3 ☐ Bilateral

5. Menopausal status at diagnosis:

   1 ☐ Premenopausal
   2 ☐ Postmenopausal ——— **6. Age at menopause:** ☐☐ years
   7 ☐ Not applicable, male patient
   8 ☐ Unknown

7. Did patient have a history of prior cancer (other than breast cancer)?

   1 ☐ Yes ———
   0 ☐ No

   8. Cite prior disease:
      1 ☐ Hodgkin lymphoma
      2 ☐ Non-Hodgkin lymphoma
      7 ☐ Other, specify: _____

   9. Date of diagnosis of prior cancer: ☐☐ ☐☐
      Month   Year

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10. Were metastases (other than ipsilateral axillary lymph nodes) present at diagnosis?

1 ☐ Yes

0 ☐ No

	Yes	No	Unknown	
11.	1 ☐	0 ☐	8 ☐	Bone
12.	1 ☐	0 ☐	8 ☐	Bone marrow
13.	1 ☐	0 ☐	8 ☐	Lung
14.	1 ☐	0 ☐	8 ☐	Liver
15.	1 ☐	0 ☐	8 ☐	Skin
16.	1 ☐	0 ☐	8 ☐	Chest wall
17.	1 ☐	0 ☐	8 ☐	Other lymph nodes, specify site: _____
18.	1 ☐	0 ☐	8 ☐	Other, specify: _____

19. Did patient receive neoadjuvant treatment (includes chemotherapy, hormones and/or radiation) prior to definitive surgery?

1 ☐ Yes

0 ☐ No — [Go to Q. 38]

Neoadjuvant Treatment

<u>Size of primary tumor (largest diameter before neoadjuvant treatment)</u>

20. Was tumor multicentric?

1 ☐ Yes

0 ☐ No

8 ☐ Unknown

<u>Give size of largest tumor in Q.21 – 22</u>

21. Clinical size: ☐☐ cm   -7 ☐ Not measurable   -8 ☐ Unknown

22. Radiographic size: ☐☐ cm   -7 ☐ Not measurable   -8 ☐ Unknown

23. Did patient receive neoadjuvant **chemotherapy**?

1 ☐ Yes

0 ☐ No

Specify chemotherapy:

	Yes	No	
24.	1 ☐	0 ☐	Adriamycin alone
25.	1 ☐	0 ☐	CAF
26.	1 ☐	0 ☐	CMF
27.	1 ☐	0 ☐	AFM
28.	1 ☐	0 ☐	Other, specify: _____

29. Number of cycles: ☐

30. Did patient receive neoadjuvant **hormone therapy**?

1 ☐ Yes

0 ☐ No

Specify hormones:

	Yes	No	
31.	1 ☐	0 ☐	Tamoxifen
32.	1 ☐	0 ☐	Other, specify: _____

33. Duration of pre-surgical treatment was: ☐☐.☐ mos.

Continued on next page

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34. Did patient receive neoadjuvant radiation therapy?

1 ☐ Yes
0 ☐ No

> **35. Specify radiation field:** _____
>
> **36. Total dose:** ☐☐☐☐ cGy (rads)

37. Best clinical response (at time of surgery) to neoadjuvant treatment:

1 ☐ Complete response
2 ☐ Partial response
3 ☐ Stable disease
4 ☐ Progressive disease
8 ☐ Not evaluable, specify why not evaluable: _____

38. Did patient have surgery as part of initial management (include surgery done after neoadjuvant treatment)?

1 ☐ Yes
0 ☐ No

> **39. Type of surgery was:**
>
> 1 ☐ Mastectomy
> 2 ☐ Lumpectomy
> 7 ☐ Other, specify: _____

<u>Size of primary tumor at time of definitive surgery; or, if surgery was not done, prior to initial non-surgical treatment</u>

40. Was tumor multicentric?

1 ☐ Yes
0 ☐ No

<u>Give size of largest tumor in Q.41 – 43</u>

41. Clinical size: ☐☐ cm   -8 ☐ Unknown

42. Radiographic size: ☐☐ cm   -8 ☐ Unknown

43. Pathologic size: ☐☐ cm   -8 ☐ Unknown

44. How many axillary nodes were examined? ☐☐   -8 ☐ Unknown

45. How many axillary nodes were positive for breast cancer? ☐☐   -8 ☐ Unknown

46. Were estrogen receptor assays done?

1 ☐ Yes
0 ☐ No
8 ☐ Unknown

> **47. Results:**
> 1 ☐ Positive   3 ☐ Borderline
> 2 ☐ Negative   8 ☐ Unknown
>
> **48. Actual value if available (specify units):** ☐☐☐☐
>
> > **49. Units:**
> > 1 ☐ fmol/mg
> > 7 ☐ Other, specify: _____

50. Were progesterone receptor assays done?

1 ☐ Yes
0 ☐ No
8 ☐ Unknown

> **51. Results:**
> 1 ☐ Positive   3 ☐ Borderline
> 2 ☐ Negative   8 ☐ Unknown
>
> **52. Actual value if available (specify units):** ☐☐☐☐
>
> > **53. Units:**
> > 1 ☐ fmol/mg
> > 7 ☐ Other, specify: _____

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54. Did patient receive radiation, chemotherapy and/or hormone treatment (excluding neoadjuvant) after definitive surgery as part of initial management?

1 □ Yes
0 □ No

55. Did patient receive radiation treatment?

1 □ Yes
0 □ No

> Radiation field:
> | | Yes | No | |
> **56.** 1 □ 0 □ local/regional
> **57.** 1 □ 0 □ sites of distant metastatic disease
> **58.** 1 □ 0 □ Other, specify: _____
>
> **59.** Total dose: □□□□ cGy (rads)

60. Did patient receive hormones?

1 □ Yes
0 □ No

> Specify hormones:
> | | Yes | No |
> **61.** 1 □ 0 □ Tamoxifen
> **62.** 1 □ 0 □ Other, specify: _____
>
> **63.** Date started: □□ □□
> Month   Year
>
> **64.** Date ended: □□ □□
> Month   Year

65. Did patient receive chemotherapy?

1 □ Yes
0 □ No

> **66.** Reason for chemotherapy:
> 1 □ Adjuvant
> 2 □ For metastatic disease ——— (Go to Q.79)
>
> Chemotherapy given:
> | | Yes | No |
> **67.** 1 □ 0 □ CMF
> **68.** 1 □ 0 □ CAF
> **69.** 1 □ 0 □ Adriamycin-containing regimen
> **70.** 1 □ 0 □ Taxol alone
> **71.** 1 □ 0 □ Taxol plus other drugs
> **72.** 1 □ 0 □ Other chemotherapy, specify:
>
> _____
>
> **73.** Number of cycles: □□   -8 □ Unknown
>
> **74.** Date started: □□ □□
> Month   Year
>
> **75.** Date ended: □□ □□
> Month   Year

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76. Did breast cancer recur?

1 ☐ Yes ——┐
0 ☐ No

> **77.** Date: ☐☐ ☐☐
>   Month Year
>
> **78.** Site(s): _____

79. Did patient receive treatment for persistent, recurrent or metastatic disease? 1 ☐ Yes   0 ☐ No

Regimen	Date Started	Date Stopped	Number cycles (chemotherapy)	Total dose (radiation)	Non-bone Response (see below)	Bone Response (see below)	Date Relapse/ Progression
1st	**80.** ☐☐ ☐☐ Month Year	**81.** ☐☐ ☐☐ Month Year	**82.** ☐☐	**83.** ☐☐☐☐☐ cGy (rads)	**84.** ☐	**85.** ☐	**86.** ☐☐ ☐☐ Month Year

Treatment, specify all drugs given:

    Yes No

87. 1☐ 0☐ Adriamycin   **91.** 1☐ 0☐ Methotrexate   **94.** 1☐ 0☐ Thiotepa
88. 1☐ 0☐ Cytoxan   **92.** 1☐ 0☐ Mitoxantrone   **95.** 1☐ 0☐ Vinblastine
89. 1☐ 0☐ Cisplatin   **93.** 1☐ 0☐ Taxol   **96.** 1☐ 0☐ Other, specify:
90. 1☐ 0☐ 5-fluorouracil (5-FU)   _____

Regimen	Date Started	Date Stopped	Number cycles	Total dose	Non-bone Response	Bone Response	Date Relapse/ Progression
2nd	**97.** ☐☐ ☐☐ Month Year	**98.** ☐☐ ☐☐ Month Year	**99.** ☐☐	**100.** ☐☐☐☐☐ cGy (rads)	**101.** ☐	**102.** ☐	**103.** ☐☐ ☐☐ Month Year

Treatment, specify all drugs given:

    Yes No

104. 1☐ 0☐ Adriamycin   **108.** 1☐ 0☐ Methotrexate   **111.** 1☐ 0☐ Thiotepa
105. 1☐ 0☐ Cytoxan   **109.** 1☐ 0☐ Mitoxantrone   **112.** 1☐ 0☐ Vinblastine
106. 1☐ 0☐ Cisplatin   **110.** 1☐ 0☐ Taxol   **113.** 1☐ 0☐ Other, specify:
107. 1☐ 0☐ 5-fluorouracil (5-FU)   _____

Regimen	Date Started	Date Stopped	Number cycles	Total dose	Non-bone Response	Bone Response	Date Relapse/ Progression
3rd	**114.** ☐☐ ☐☐ Month Year	**115.** ☐☐ ☐☐ Month Year	**116.** ☐☐	**117.** ☐☐☐☐☐ cGy (rads)	**118.** ☐	**119.** ☐	**120.** ☐☐ ☐☐ Month Year

Treatment, specify all drugs given:

    Yes No

121. 1☐ 0☐ Adriamycin   **125.** 1☐ 0☐ Methotrexate   **128.** 1☐ 0☐ Thiotepa
122. 1☐ 0☐ Cytoxan   **126.** 1☐ 0☐ Mitoxantrone   **129.** 1☐ 0☐ Vinblastine
123. 1☐ 0☐ Cisplatin   **127.** 1☐ 0☐ Taxol   **130.** 1☐ 0☐ Other, specify:
124. 1☐ 0☐ 5-fluorouracil (5-FU)   _____

Non-bone response codes:
1 = CR
2 = PR
3 = stable disease
4 = progressive disease

Bone response codes:
1 = no prior bone disease
2 = symptomatic improvement, no progression
3 = symptomatic and radiographic (not bone scan only) improvement
4 = no response
5 = progressive disease
6 = not evaluable (radiographic data not available)

Continued on next page

Regimen	Date Started	Date Stopped	Number cycles (chemotherapy)	Total dose (radiation)	Non-bone Response (see below)	Bone Response (see below)	Date Relapse/ Progression
	131.	**132.**	**133.**	**134.**	**135.**	**136.**	**137.**
4th	☐☐ ☐☐	☐☐ ☐☐	☐☐	☐☐☐☐ cGy (rads)	☐	☐	☐☐ ☐☐
	Month Year	Month Year					Month Year

Treatment, specify all drugs given:

Yes No
- **138.** 1☐ 0☐ Adriamycin
- **139.** 1☐ 0☐ Cytoxan
- **140.** 1☐ 0☐ Cis-platin
- **141.** 1☐ 0☐ 5-fluorouracil (5-FU)

- **142.** 1☐ 0☐ Methotrexate
- **143.** 1☐ 0☐ Mitoxantrone
- **144.** 1☐ 0☐ Taxol

- **145.** 1☐ 0☐ Thiotepa
- **146.** 1☐ 0☐ Vinblastine
- **147.** 1☐ 0☐ Other, specify: _____

Regimen	Date Started	Date Stopped	Number cycles	Total dose	Non-bone Response	Bone Response	Date Relapse/ Progression
	148.	**149.**	**150.**	**151.**	**152.**	**153.**	**154.**
5th	☐☐ ☐☐	☐☐ ☐☐	☐☐	☐☐☐☐ cGy (rads)	☐	☐	☐☐ ☐☐
	Month Year	Month Year					Month Year

Treatment, specify all drugs given:

Yes No
- **155.** 1☐ 0☐ Adriamycin
- **156.** 1☐ 0☐ Cytoxan
- **157.** 1☐ 0☐ Cis-platin
- **158.** 1☐ 0☐ 5-fluorouracil (5-FU)

- **159.** 1☐ 0☐ Methotrexate
- **160.** 1☐ 0☐ Mitoxantrone
- **161.** 1☐ 0☐ Taxol

- **162.** 1☐ 0☐ Thiotepa
- **163.** 1☐ 0☐ Vinblastine
- **164.** 1☐ 0☐ Other, specify: _____

Non-bone response codes:
1 = CR
2 = PR
3 = stable disease
4 = progressive disease

Bone response codes:
1 = no prior bone disease
2 = symptomatic improvement, no progression
3 = symptomatic and radiographic (not bone scan only) improvement
4 = no response
5 = progressive disease
6 = not evaluable (radiographic data not available)

What was the total dose of anthracyclines prior to start of high-dose therapy (conditioning)?

165. Doxorubicin: ☐☐☐ mg/m² -8 ☐ Unknown -7 ☐ Not given
(Adriamycin)

166. Mitoxantrone: ☐☐☐ mg/m² -8 ☐ Unknown -7 ☐ Not given

167. Other ☐☐☐ mg/m² -8 ☐ Unknown -7 ☐ Not given
anthracycline, specify: _____

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168. Was bone marrow biopsy done <u>prior to high-dose conditioning</u>?

₁ ☐ Yes ———
₀ ☐ No

> **169.** Date of most recent biopsy   ☐☐ ☐☐ ☐☐
>   Month Day Year
>
> **170.** Was breast cancer present?
>
>   ₁ ☐ Yes ———
>   ₀ ☐ No
>
> > How was it detected?
> > | | Yes | No | Not tested | |
> > |---|---|---|---|---|
> > | **171.** | ₁☐ | ₀☐ | ₇☐ | Routine histopathology |
> > | **172.** | ₁☐ | ₀☐ | ₇☐ | PCR (polymerase chain reaction) |
> > | **173.** | ₁☐ | ₀☐ | ₇☐ | Other molecular technique |
> > | **174.** | ₁☐ | ₀☐ | ₇☐ | Immunohistochemistry |
> > | **175.** | ₁☐ | ₀☐ | ₇☐ | Cell culture technique |
> > | **176.** | ₁☐ | ₀☐ | ₇☐ | Other, specify: _____ |

177. Did patient <u>ever</u> have bone marrow involvement with breast cancer other than involvement indicated in Q.168?

₁ ☐ Yes ———
₀ ☐ No

> How was it detected?
> | | Yes | No | Not tested | |
> |---|---|---|---|---|
> | **178.** | ₁☐ | ₀☐ | ₇☐ | Routine histopathology |
> | **179.** | ₁☐ | ₀☐ | ₇☐ | PCR (polymerase chain reaction) |
> | **180.** | ₁☐ | ₀☐ | ₇☐ | Other molecular technique |
> | **181.** | ₁☐ | ₀☐ | ₇☐ | Immunohistochemistry |
> | **182.** | ₁☐ | ₀☐ | ₇☐ | Cell culture technique |
> | **183.** | ₁☐ | ₀☐ | ₇☐ | Other, specify: _____ |

184. What was status of disease <u>immediately prior to start of conditioning</u>?

₁ ☐ Complete response - no evidence of disease
₂ ☐ Complete response with exception of bone scan
     abnormalities of unknown significance
₃ ☐ Partial response
₄ ☐ Stable
₅ ☐ Progressive disease

Indicate all sites of disease involvement:

	At any time between diagnosis and transplant				Immediately prior to start of conditioning		
		Yes	No	Unknown		Yes	No	Unknown
Breast	**185.1.**	₁☐	₀☐	₈☐	**185.2.**	₁☐	₀☐	₈☐
Chest wall	**186.1.**	₁☐	₀☐	₈☐	**186.2.**	₁☐	₀☐	₈☐
Bone - symptomatic	**187.1.**	₁☐	₀☐	₈☐	**187.2.**	₁☐	₀☐	₈☐
Bone - radiographic	**188.1.**	₁☐	₀☐	₈☐	**188.2.**	₁☐	₀☐	₈☐
Axillary lymph nodes	**189.1.**	₁☐	₀☐	₈☐	**189.2.**	₁☐	₀☐	₈☐
Other lymph nodes	**190.1.**	₁☐	₀☐	₈☐	**190.2.**	₁☐	₀☐	₈☐
Brain	**191.1.**	₁☐	₀☐	₈☐	**191.2.**	₁☐	₀☐	₈☐
Lung	**192.1.**	₁☐	₀☐	₈☐	**192.2.**	₁☐	₀☐	₈☐
Pleura	**193.1.**	₁☐	₀☐	₈☐	**193.2.**	₁☐	₀☐	₈☐
Liver	**194.1.**	₁☐	₀☐	₈☐	**194.2.**	₁☐	₀☐	₈☐
Skin	**195.1.**	₁☐	₀☐	₈☐	**195.2.**	₁☐	₀☐	₈☐
Other, specify:	**196.1.**	₁☐	₀☐	₈☐	**196.2.**	₁☐	₀☐	₈☐

TEAM □□□□ IUBMID □□□□□□

197. What was sensitivity of breast cancer to chemotherapy prior to conditioning? *(Response to last chemotherapy given prior to transplant; chemotherapy must include ≥ 2 cycles treatment given ≤ 6 months prior to transplant)*

1 □ Sensitive: ≥ 50% reduction in bidimensional diameter of all disease sites with no new sites of disease

2 □ Resistant: < 50% reduction in diameter of all disease sites or development of new disease sites

3 □ Untreated

8 □ Unknown

Outcome

198. What was patient's best response to transplant <u>excluding</u> planned posttransplant treatment?

1 □ Complete response: complete disappearance of all known disease for ≥ 4 weeks

2 □ Complete response with persistent bone scan/x-ray abnormalities of unknown significance

3 □ Partial response: ≥ 50% reduction in greatest diameter of all sites of known disease and no new sites of disease for ≥ 4 weeks

4 □ No response: < 50% reduction in greatest diameter of all sites of known disease and no new sites of disease

5 □ Progressive disease: increase in size of sites of known disease or new sites of disease

6 □ Not evaluable, toxic death

7 □ Not evaluable, other reason, specify: _____

199. Was planned treatment (treatment before progressive disease) given <u>posttransplant</u>?

1 □ Yes ——

0 □ No

⌐ Go to Q.207 ⌐

200. Was disease restaged prior to planned posttransplant treatment?

1 □ Yes

0 □ No

<u>Specify treatment given whether restaged or not:</u>

    <u>Yes</u> <u>No</u>

201. 1 □ 0 □ Chemotherapy, specify: _____

202. 1 □ 0 □ Hormone therapy, specify: _____

203. 1 □ 0 □ Radiation therapy, specify: _____

204. 1 □ 0 □ Immune therapy, specify: _____

205. 1 □ 0 □ Other, specify: _____

206. What was patient's best response to transplant <u>including</u> planned posttransplant treatment?

1 □ Complete response: complete disappearance of all known disease for ≥ 4 weeks

2 □ Complete response with persistent bone scan/x-ray abnormalities of unknown significance

3 □ Partial response: ≥ 50% reduction in greatest diameter of all sites of known disease and no new sites of disease for ≥ 4 weeks

4 □ No response: < 50% reduction in greatest diameter of all sites of known disease and no new sites of disease

5 □ Progressive disease: increase in size of sites of known disease or new sites of disease

6 □ Not evaluable, toxic death

7 □ Not evaluable, other reason, specify: _____

207. Status of breast cancer: (*at time of this report or at time of death*)

   1 ☐ Free of breast cancer; no recurrence posttransplant

   2 ☐ Free of breast cancer except for persistent scan abnormalities of unknown significance, no recurrence posttransplant

   3 ☐ Persistent breast cancer without progression (*never achieved complete response*)

   4 ☐ Progressive disease (*never achieved complete response*)

> Date of progression ☐☐ ☐☐ ☐☐   Site(s): _____
>   Month Day Year

   5 ☐ Recurrent disease (relapse after complete response)

> Date of recurrence ☐☐ ☐☐ ☐☐   Site(s): _____
>   Month Day Year

   6 ☐ Free of breast cancer after posttransplant recurrence

> Date of recurrence ☐☐ ☐☐ ☐☐   Site(s): _____
>   Month Day Year

   7 ☐ Not evaluable; explain: _____

First site(s) of progression/recurrence:

	Yes	No	
208.	1 ☐	0 ☐	Lymph node
209.	1 ☐	0 ☐	Bone marrow
210.	1 ☐	0 ☐	CNS
211.	1 ☐	0 ☐	Liver
212.	1 ☐	0 ☐	Lung
213.	1 ☐	0 ☐	Local
214.	1 ☐	0 ☐	Contralateral breast
215.	1 ☐	0 ☐	Other, specify: _____

216. Date status established: ☐☐ ☐☐ ☐☐
                              Month Day Year

TEAM ☐☐☐☐ IUBMID ☐☐☐☐☐☐☐

*(Institutional Unique Blood or Marrow
Transplant Identification Number)*

Date of transplant for which
this form is being completed: ☐☐ ☐☐ ☐☐
Month Day Year

Date of report: ☐☐ ☐☐ ☐☐
Month Day Year

Follow-up Information

*** *Report data for date of last contact as reported in Q.3 of Follow-up Core Form or
immediately prior to death.***

1. Was <u>planned</u> post transplant treatment (treatment before progressive disease) given since date of last report?

1 ☐ Yes ——
0 ☐ No

[Go to Q.9]

2. Was disease restaged prior to planned posttransplant treatment?

1 ☐ Yes

0 ☐ No

<u>Specify treatment given whether restaged or not:</u>
    Yes No
3. 1☐ 0☐ Chemotherapy, specify: _____
4. 1☐ 0☐ Hormone therapy, specify: _____
5. 1☐ 0☐ Radiation therapy, specify: _____
6. 1☐ 0☐ Immune therapy, specify: _____
7. 1☐ 0☐ Other, specify: _____

8. Specify best response to transplant <u>including</u> planned posttransplant treatment:

1 ☐ Complete response (*complete disappearance of all known disease for ≥ 4 weeks*)

2 ☐ Complete response with persistent bone scan or x-ray abnormalities of unknown significance

3 ☐ Partial response (*≥ 50% reduction in greatest diameter of all sites of known disease and no new sites of disease
for ≥ 4 weeks*)

4 ☐ No response: < 50% reduction in greatest diameter of all sites of known disease and no new sites of disease

5 ☐ Progressive disease: increase in size of sites of known disease or new sites of disease
    Specify site(s) of persistent/new disease: _____

6 ☐ Not evaluable, toxic death

7 ☐ Not evaluable, other reason, specify: _____

TEAM ☐☐☐☐   IUBMID ☐☐☐☐☐☐

9. Most recent status of breast cancer: *(for patients who died, report status at time of death)*

   1 ☐ Free of breast cancer; no recurrence posttransplant

   2 ☐ Free of breast cancer except for persistent scan abnormalities of unknown significance, no recurrence posttransplant

   3 ☐ Persistent breast cancer without progression *(never achieved CR or PR)*

   4 ☐ Progressive disease *(never achieved CR or PR)*

Date of progression	☐☐	☐☐	☐☐	Site(s): _____
	Month	Day	Year	

   5 ☐ Recurrent disease (relapse after complete remission)

Date of progression	☐☐	☐☐	☐☐	Site(s): _____
	Month	Day	Year	

   6 ☐ Free of breast cancer after posttransplant recurrence

Date of recurrence	☐☐	☐☐	☐☐	Site(s): _____
	Month	Day	Year	

   7 ☐ Not evaluable; explain: _____

10. Date current status established   ☐☐ ☐☐ ☐☐

                                         Month   Day   Year

<u>First</u> site(s) of progression/recurrence:

	Yes	No	
11.	1 ☐	0 ☐	Lymph node
12.	1 ☐	0 ☐	Bone marrow
13.	1 ☐	0 ☐	CNS
14.	1 ☐	0 ☐	Liver
15.	1 ☐	0 ☐	Lung
15.2	1 ☐	0 ☐	Local (chest wall)
15.3	1 ☐	0 ☐	Contralateral breast
16.	1 ☐	0 ☐	Other, specify:_____

Transplant Essential Data
First Report: 100 Days Post Transplant

Primary Disease Diagnosis: _____

_____

Graft: ☐ Auto ☐ Allo ☐ Syngeneic

Date of This Report:___ ___ ___ ___ - ___ ___ - ___ ___
         YYYY   MM   DD

PATIENT IDENTIFICATION

Hospital Unique Patient Number: _____

Last/Family Name: _____

First/Given Name: _____

~or~ Initials:_____ _____
         First Name   Last Name

Date of Birth:___ ___ ___ ___ - ___ ___ - ___ ___
         YYYY   MM   DD

Sex: ☐ Male   ☐ Female

Ethnicity: ☐ White/Caucasian ☐ Black ☐ Oriental
           ☐ Other, specify: _____

Postal Code of Patient's Residence: _____

DISEASE
(complete appropriate disease classification sheet)
Date of initial diagnosis of primary disease:

___ ___ ___ ___ - ___ ___ - ___ ___
      YYYY   MM   DD

TRANSPLANTATION

Date of this transplant:___ ___ ___ ___ - ___ ___ - ___ ___
            YYYY   MM   DD

Chronological number of this transplant for this patient:_____

If >1, date of most recent previous transplant for this patient:

___ ___ ___ ___ - ___ ___ - ___ ___
      YYYY   MM   DD

Source of Stem Cells (check all that apply):
 ☐ Bone marrow   ☐ Peripheral blood
 ☐ Cord blood   ☐ Other: _____

Donor Type (check one):
 ☐ Autologous (self)   ☐ Syngeneic(monozygotic twin)
 Allogeneic:
 ☐ HLA-identical sibling (not monozygotic twin)
 ☐ HLA-matched other relative
 ☐ HLA-mismatched sibling or other relative
 ☐ HLA-matched unrelated donor
 ☐ HLA-mismatched unrelated donor
 ☐ Multiple donors

(For allotransplants) donor sex: ☐ Male ☐ Female

Was the graft manipulated ex vivo other than for RBC removal or volume reduction? ☐ Yes ☐ No

Was this transplant part of a planned sequential transplant protocol? ☐ Yes ☐ No

Additional cell therapy given? ☐ Yes ☐ No ☐ Unknown

 If yes, type of cell(s) (check all that apply):
 ☐ Lymphocytes   ☐ Fibroblasts   ☐ Dendritic cells
 ☐ Other: _____

 If yes, date of first infusion of additional cell therapy (may be the same as transplant date):

___ ___ ___ ___ - ___ ___ - ___ ___
      YYYY   MM   DD

CENTRE IDENTIFICATION
Centre Identification Code:
        EBMT _____
     IBMTR/ABMTR _____
National (specify) _____
     Other (specify) _____
Hospital: _____
Unit: _____
Contact person: _____
Phone #: _____
Fax #: _____
Email: _____

BEFORE TRANSPLANTATION
Performance Score Pretransplant:
 ☐ Good (KPS ≥80 ~or~ ECOG 0-1 ~or~ Lansky ≥80)
 ☐ Poor (KPS <80 ~or~ ECOG 2-4 ~or~ Lansky <80)
Did conditioning regimen contain Total Body Irradiation?
 ☐ Yes ☐ No

AFTER TRANSPLANTATION
Engraftment (Neutrophils ≥0.5 x 10^9/L)?
 ☐ Yes ☐ No ☐ Unknown
 If yes, date Neutrophils ≥0.5 x 10^9/L:

___ ___ ___ ___ - ___ ___ - ___ ___
      YYYY   MM   DD
 If no, date of latest assessment:

___ ___ ___ ___ - ___ ___ - ___ ___
      YYYY   MM   DD

Maximum Grade of Acute Graft Versus Host Disease (GVHD):
 ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ Unknown ☐ NA
Best disease response to transplant:
 ☐ Continued CR   ☐ CR achieved, date achieved:

___ ___ ___ ___ - ___ ___ - ___ ___
      YYYY   MM   DD

 ☐ Never in CR, date assessed:
 ☐ Unknown   ___ ___ ___ ___ - ___ ___ - ___ ___
              YYYY   MM   DD

Did the disease for which the patient was transplanted relapse or progress after the transplant?
 ☐ Yes ☐ No ☐ Unknown
 If yes, check all that apply to describe relapse/progression:
 ☐ Molecular   ☐ Cytogenetic   ☐ Hematological/Clinical
 If yes, date of earliest relapse or progression:

___ ___ ___ ___ - ___ ___ - ___ ___
      YYYY   MM   DD
 If no, date of latest assessment:

___ ___ ___ ___ - ___ ___ - ___ ___
      YYYY   MM   DD

Survival status after transplant:
 ☐ Alive ☐ Dead ☐ Died before transplant
 Date of latest follow-up or death:

___ ___ ___ ___ - ___ ___ - ___ ___
      YYYY   MM   DD

Main cause of death (check one):
 ☐ Relapse or Progression
   Transplantation related causes:
   ☐ Rejection/Poor graft function   ☐ GVHD
   ☐ Pulmonary toxicity   ☐ Cardiac toxicity
   ☐ Infection   ☐ VOD
   ☐ Posttransplant lymphoproliferative disorder ☐ Other: _____
 ☐ Other: _____
 ☐ Unknown

ACUTE LEUKEMIAS

Classification:

Acute Myelogenous Leukemia (AML)
- ❑ M1
- ❑ M2
- ❑ M3
- ❑ M4
- ❑ M5
- ❑ M6
- ❑ M7
- ❑ AML unspecified
- ❑ Other,
  specify:_____

Acute Lymphoblastic Leukemia (ALL)
- ❑ ALL B-lineage
- ❑ ALL T-lineage
- ❑ Mature B cell (L3)
- ❑ ALL unspecified
- ❑ Other,
  specify:_____

Other Acute Leukemias
- ❑ Acute undifferentiated
- ❑ Acute biphenotypic
- ❑ Acute mast cell leukemia
- ❑ Other,
  specify:_____

Status at Transplantation:

- ❑ Primary Induction Failure (PIF)
- ❑ CR 1
- ❑ Rel 1
- ❑ CR 2-
- ❑ Rel 2-

For Complete Remission

Y	N	Unk	
❑	❑	❑	Hematological remission
❑	❑	❑	Cytogenetic remission
❑	❑	❑	Molecular remission

CHRONIC MYELOGENOUS LEUKEMIA (CML)

Classification:

- ❑ Juvenile CML
- ❑ CML, Ph+
- ❑ CML, Ph-
- ❑ CML, not otherwise specified

Status at Transplantation:

- ❑ CP 1
- ❑ CP 2+
- ❑ AP
- ❑ BP

Chronic Phase Only *(check all that apply)*
- ❑ Stable, not hematological remission
- ❑ Hematological remission
- ❑ Partial cytogenetic remission
- ❑ Complete cytogenetic remission
- ❑ Molecular remission
- ❑ Cytogenetics unknown
- ❑ bcr/abl unknown

OTHER LEUKEMIAS

Classification:

- ❑ Chronic Lymphoblastic Leukemia (CLL), B-cell
- ❑ CLL, T-cell
- ❑ CLL, not otherwise specified

- ❑ Prolymphocytic Leukemia
- ❑ Hairy Cell Leukemia
- ❑ Other leukemia,
  specify:_____

Status at Transplantation:

- ❑ CR
- ❑ PR
- ❑ No response/stable
- ❑ Progression

CR=complete remission, PR=partial remission, Rel=relapse, CP=chronic phase, AP accelerated phase, BP=blast phase

MYELODYSPLASTIC MYELOPROLIFERATIVE SYNDROMES

Classification:

Myelodysplastic Syndromes (MDS)
- ❑ RA
- ❑ RAEB
- ❑ RAEB-t
- ❑ CMMoL
- ❑ RARS
- ❑ MDS not otherwise specified
- ❑ Other,
  specify:_____

Myeloproliferative Syndromes (MPS)
- ❑ Polycythemia vera
- ❑ Essential or primary thrombocythemia
- ❑ Myelofibrosis with myeloid metaplasia
- ❑ Acute myelofibrosis or myelosclerosis
- ❑ Paroxysmal nocturnal hemoglobinuria
- ❑ MPS not otherwise specified
- ❑ Other,
  specify:_____

Status at Transplantation:

- ❑ Untreated
- ❑ Treatment with intent to achieve a CR – CR not achieved
- ❑ Treatment with intent to achieve a CR – CR achieved
- ❑ Relapse after CR

ANEMIA/HEMOGLOBINOPATHY

Classification:

- ❑ Acquired Severe Aplastic Anemia (SAA), not otherwise specified
- ❑ Acquired SAA, secondary to hepatitis
- ❑ Acquired SAA, secondary to toxin/other drug
- ❑ Amegakaryocytosis acquired (not congenital)
- ❑ Acquired Pure Red Cell Aplasia (PRCA) (not congenital)
- ❑ Other acquired cytopenic syndrome,
  specify:_____
- ❑ Fanconi anemia
- ❑ Diamond-Blackfan anemia (congenital PRCA)
- ❑ Other constitutional anemia,
  specify:_____
- ❑ Thalassemia
- ❑ Sickle cell disease
- ❑ Other hemoglobinopathy,
  specify:_____

PLATELET DISORDERS

Classification:

- ❑ Amegakaryocytosis/congenital thrombocytopenia
- ❑ Glanzmann thrombasthenia
- ❑ Other inherited platelet abnormalities,
  specify:_____

HISTIOCYTIC DISORDERS

Classification:

- ❑ Histiocytic disorders, not otherwise specified
- ❑ Familial erythro/hemophagocytic lymphohistiocytosis(FELH)
- ❑ Histiocytosis-X
- ❑ Hemophagocytosis (reactive or viral associated)
- ❑ Malignant histiocytosis
- ❑ Other, specify:_____

CR=complete remission

LYMPHOMAS

Classification:

Hodgkin Disease
- ❏ Lymphocyte predominant
- ❏ Nodular sclerosis
- ❏ Mixed celluarity
- ❏ Lymphocyte depleted
- ❏ Hodgkin disease, not otherwise specified
- ❏ Other,
    specify:_____

Non-Hodgkin Lymphoma (NHL)
- ❏ Follicular NHL
- ❏ Mantle cell NHL
- ❏ Marginal zone B-cell lymphoma of mucosa-associated tissue (MALT)
- ❏ Diffuse large B-cell NHL, centroblastic
- ❏ Diffuse large B-cell NHL, immunoblastic
- ❏ Diffuse large B-cell NHL, anaplastic
- ❏ Lymphoblastic/Burkitt
- ❏ Precursor B-cell lymphoblastic
- ❏ Angioblastic T-cell NHL
- ❏ Peripheral T-cell NHL
- ❏ Anaplastic large cell, T-cell and null cell
- ❏ Precursor T-cell lymphoblastic
- ❏ NHL, not otherwise specified
- ❏ Other,
    specify:_____

Status at Transplantation:

- ❏ At diagnosis
- ❏ Primary Induction Failure (PIF)
- ❏ CR 1
- ❏ CR 2
- ❏ CR 3+
- ❏ Rel 1
- ❏ Rel 2+

For Relapses & PIF
- ❏ Sensitive
- ❏ Resistant
- ❏ Untreated
- ❏ Unknown

PLASMA CELL DISORDERS

Classification:

- ❏ Multiple myeloma-Ig
- ❏ Multiple myeloma-IgA
- ❏ Multiple myeloma-IgD
- ❏ Multiple myeloma-IgE
- ❏ Multiple myeloma-light chain
- ❏ Multiple myeloma-non-secretory
- ❏ Multiple myeloma, not otherwise specified
- ❏ Plasma cell leukemia
- ❏ Solitory plasmacytoma
- ❏ Waldenstrom's macroglobulinemia
- ❏ Amyloidosis
- ❏ Other,
    specify:_____

Stage at Diagnosis
(Multiple Myeloma only)
- ❏ 1 and ❏ A
- ❏ 2   ❏ B
- ❏ 3

Status at Transplantation:

- ❏ CR
- ❏ PR
- ❏ MR
- ❏ No change/Stable
- ❏ Progression/Relapse

Number of remissions, relapses or progressions
- ❏ 1st
- ❏ 2nd
- ❏ >2nd

CR=complete remission, PR=partial remission, Rel=relapse, MR=minimal response

BREAST CANCER

Classification:

Breast Cancer
- ❑ Inflammatory
- ❑ Non-inflammatory

<u>Stage at Diagnosis</u>
(Breast Cancer only)
- ❑ II
- ❑ III
- ❑ Inflammatory, no distant metastases
- ❑ Metastatic

Status at Transplantation:

- ❑ Adjuvant (Stage II, III, inflamm)
- ❑ Metastatic

<u>For Metastatic</u>
- ❑ Untreated/Upfront
- ❑ Refractory
- ❑ CR
- ❑ PR
- ❑ Unknown

<u>For Metastatic</u>
Patient had a prior CR?
- ❑ Yes
- ❑ No

OTHER MALIGNANCIES

Classification:

- ❑ Head and neck
- ❑ Lung cancer, small cell
- ❑ Lung cancer, non-small cell
- ❑ Lung cancer, not otherwise specified
- ❑ Thymoma
- ❑ Gastric
- ❑ Colorectal
- ❑ Pancreas
- ❑ Hepatobiliary
- ❑ Kidney and urinary tract
- ❑ Wilm tumour
- ❑ Prostate
- ❑ Testicular
- ❑ External genitalia
- ❑ Cervical
- ❑ Uterus
- ❑ Ewing sarcoma
- ❑ Ovary
- ❑ Vagina
- ❑ Germ cell tumour

- ❑ Sarcoma not otherwise specified
- ❑ Soft tissue sarcoma
- ❑ Bone sarcoma (excluding Ewing sarcoma)
- ❑ Rhabdomyosarcoma
- ❑ Leiomyosarcoma
- ❑ Liposarcoma
- ❑ Fibrosarcoma
- ❑ Synovial sarcoma
- ❑ Hemanglosarcoma
- ❑ Lymphanglosarcoma
- ❑ Neurogenic sarcoma
- ❑ Melanoma
- ❑ Central nervous system tumors
- ❑ Medulloblastoma
- ❑ Neuroblastoma
- ❑ Retinoblastoma
- ❑ PNET
- ❑ Other
  specify:_____

Status at Transplantation:

- ❑ Primary refractory
- ❑ CR
- ❑ VGPR
- ❑ PR
- ❑ MR
- ❑ Relapse
- ❑ Primary treatment
- ❑ Adjuvant

<u>For Responses</u>
- ❑ 1st
- ❑ 2nd
- ❑ >2nd

<u>For Relapses</u>
- ❑ Sensitive
- ❑ Resistant
- ❑ Untreated
- ❑ Unknown

CR=complete remission, PR=partial remission, VGPR=very good partial response, MR=minimal response

INHERITED DISORDERS OF METABOLISM

Classification:

❑ Osteopetrosis (malignant infantile osteopetrosis)
❑ Lesch-Nyhan (HGPRT deficiency)
❑ Neuronal ceriod lipifuscinosis (Batten disease)
❑ Mucopolysaccharidosis, NOS
❑ Hurler syndrome (IH)
❑ Scheie syndrome (IS)
❑ Hunter syndrome (II)
❑ San Filippo (III)
❑ Morquio (IV)
❑ Maroteaux-Lamy (VI)
❑ B-glucuronidase deficiency (VII)
❑ Mucopolysaccharidosis (V)
❑ Mucolipidioses, NOS
❑ Gaucher's disease

❑ Metachromatic leukodystrophy
❑ Adrenoleukodystrophy
❑ Krabbe disease (globoid leukodystrophy)
❑ Neiman-Pick disease
❑ I-cell disease
❑ Wolman disease
❑ Glucose storage disease
❑ Polysaccharide hydrolase abnormalities, NOS
❑ Aspartyl glucosaminuria
❑ Fucosidosis
❑ Mannosidosis
❑ Inherited Disorders of Metabolism, not otherwise specified
❑ Other,
  specify:_____

IMMUNE DEFICIENCIES

Classification:

❑ ADA deficiency severe combined immune deficiency (SCID)
❑ Absence of T and B cells SCID
❑ Absence of T, normal B cell SCID
❑ Omenn syndrome
❑ Reticular dysgenesis
❑ Bare lymphocyte syndrome
❑ SCID, not otherwise specified
❑ SCID other,
  specify:_____
❑ Ataxia telangiectasia
❑ HIV infection
❑ Wiskott Aldrich syndrome
❑ DiGeorge anomaly
❑ Chronic granulomatous disease
❑ Chediak-Higashi syndrome
❑ Common variable immunodeficiency
❑ X-linked lymphoproliferative syndrome
❑ Leukocyte adhesion deficiencies
❑ Kostmann syndrome-congenital neutropenia
❑ Neutrophil actin deficiency
❑ Cartilage hair hypoplasia
❑ CD 40 Ligand deficiency
❑ Immune Deficiencies, not otherwise specified
❑ Other,
  specify:_____

AUTOIMMUNE DISORDERS – I

	Involved Organs/Clincal Problem	Reason for Transplant	Miscellaneous	
❑ Scleroderma	❑ diffuse cutaneous	❑	Scl 70 positive	❑
	❑ limited cutaneous	❑	ACA positive	❑
	❑ lung parenchyma	❑		
	❑ pulm. hypertension	❑		
	❑ syst. hypertension	❑		
	❑ renal (biopsy type:_____)	❑		
	❑ oesophagus	❑		
	❑ other GIT	❑		
	❑ Raynaud	❑		
	❑ CREST	❑		
	❑ other (state:_____)	❑		
❑ Systemic lupus erythematosus	❑ renal (biopsy type:_____)	❑	ds DNA	❑ (____)
	❑ CNS (type:_____)	❑	complement	❑ (____)
	❑ PNS (type:_____)	❑	other	❑ (____)
	❑ lung	❑		
	❑ serositis	❑		
	❑ arthritis	❑		
	❑ skin (type:_____)	❑		
	❑ haematological (type:_____)	❑		
	❑ vasculitis (type:_____)	❑		
	❑ other (state:_____)	❑		
❑ Sjoegran syndrome	❑ SICCA	❑		
	❑ exocrine gland swelling	❑		
	❑ other organ lymphocytic infiltration	❑		
	❑ lymphoma, paraproteinacmia	❑		
	❑ other (type:_____)	❑		
❑ Antiphospholipid syndrome	❑ thrombosis (type:_____)	❑	anticardiolpin IgG	❑
	❑ CNS (type:_____)	❑	anticardiolpin IgM	❑
	❑ abortion	❑		
	❑ skin (livido, vasculitis)	❑		
	❑ heamatological (type:_____)	❑		
	❑ other (type:_____)	❑		
❑ Polymyositis-dermatomyositis	❑ proximal weakness	❑	CPK	❑
	❑ generalized weakness (including bulbar)	❑	typical biopsy	❑
	❑ pulmonary fibrosis	❑	typical EmG	❑
	❑ vasculitis (type:_____)	❑	typical rash (DM)	❑
	❑ malignancy (type:_____)	❑		
	❑ other (type:_____)	❑		
❑ Polyarteritis nodosa	❑ renal (type:_____)	❑		
	❑ mononcuritis multiplex	❑	p-ANICA positive	❑
	❑ pulmonary heamorrage	❑	c-ANA positive	❑
	❑ GIT	❑	hepatitis serology	❑
	❑ skin	❑		
	❑ other (state:_____)	❑		

AUTOIMMUNE DISORDERS –II			
	Involved Organs/Clincal Problem	Reason for Transplant	Miscellaneous
❑ Wegener granulomatosis	❑ upper respiratory ract	❑	c-ANCA positive ❑
	❑ pulmonary	❑	
	❑ renal (biopsy type:_____)	❑	
	❑ skin	❑	
	❑ other (state:_____)	❑	
❑ Other vasculitis	❑ Churg-Strauss	❑	
	❑ Giant cell arthritis	❑	
	❑ Takayasu	❑	
	❑ Bechet	❑	
	❑ overlap nercrotising arteritis	❑	
	❑ other: (_____)	❑	
❑ Rheumatoid arthritis	❑ destructive arthritis	❑	
	❑ nercrotising vasculitis	❑	
	❑ eye (type:_____)	❑	
	❑ pulmonary	❑	
	❑ extrarticular (state:_____)	❑	
	❑ other: (_____)	❑	
❑ Psoriatic arthritis/psoriasis	❑ destructive arthritis	❑	
	❑ psoriasis	❑	
	❑ other (state:_____)	❑	
❑ Juvenile RA	❑ systemic (main feature:_____)	❑	
	❑ pauci, ANA positive (eye)	❑	
	❑ polyarticular	❑	
	❑ other (state:_____)	❑	
❑ Multiple sclerosis	❑ primary progressive	❑	
	❑ secondary progresive	❑	
	❑ relapsing/reuniting	❑	
❑ Other, specify:	❑ Inflammatory bowel disease	❑	
	❑ Myasthenia gravis	❑	
	❑ Idiopathic thrombocytopenic purpura (ITP)	❑	
	❑ Hemolytic anemic	❑	
	❑ Evan syndrome	❑	
	❑ other autoimmune cytopenia specify:_____	❑	

Transplant Essential Data
Follow-up Report: 1 Year Post Transplant and Annually

IBMTR/ABMTR

PATIENT IDENTIFICATION

Hospital Unique Patient Number: _____

Last/Family Name: _____

First/Given Name: _____

~ **or** ~ Initials: _____ _____
First Name   Last Name

Date of Birth:___ ___ ___ ___ - ___ ___ - ___ ___
YYYY   MM   DD

Sex: ❑ Male   ❑ Female

AFTER TRANSPLANTATION

Engraftment (Neutrophils $\geq 0.5 \times 10^9$/L) achieved?
❑ Yes ❑ No ❑ Unknown

If yes, date Neutrophils$\geq 0.5 \times 10^9$/L:

___ ___ ___ ___ - ___ ___ - ___ ___
YYYY   MM   DD

If no, date of latest assessment:

___ ___ ___ ___ - ___ ___ - ___ ___
YYYY   MM   DD

Did late graft failure occur? ❑ Yes ❑ No

Maximum Grade of Acute Graft Versus Host Disease (GVHD):
❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ Unknown

Best disease status post-transplant:
❑ Continued CR   ❑ CR achieved, date achieved:

___ ___ ___ ___ - ___ ___ - ___ ___
YYYY   MM   DD

❑ Never in CR, date assessed:

___ ___ ___ ___ - ___ ___ - ___ ___
YYYY   MM   DD

❑ Unknown

Did the disease for which the patient was transplanted relapse or progress after the transplant?
❑ Yes ❑ No ❑ Unknown
❑ A relapse or progression was previously reported

If yes, check all that apply to describe relapse/progression:
❑ Molecular ❑ Cytogenetic ❑ Hematological/Clinical

If yes, date of earliest relapse:

___ ___ ___ ___ - ___ ___ - ___ ___
YYYY   MM   DD

Maximum extent of Chronic GVHD:
❑ None ❑ Limited ❑ Extensive ❑ Unknown

Current disease status:
❑ Complete remission   ❑ Not in remission

Date of latest disease assessment:

___ ___ ___ ___ - ___ ___ - ___ ___
YYYY   MM   DD

CENTRE IDENTIFICATION

Centre Identification Code:

    EBMT _____

    IBMTR/ABMTR _____

National (specify) _____

    Other (specify) _____

Hospital: _____

Unit: _____

Contact person: _____

Phone #: _____

Fax #: _____

Email: _____

Date of this Report:___ ___ ___ ___ - ___ ___ - ___ ___
YYYY   MM   DD

SURVIVAL

Survial status at latest follow-up:
❑ Alive ❑ Dead ❑ Unknown

Date of latest follow-up or death:

___ ___ ___ ___ - ___ ___ - ___ ___
YYYY   MM   DD

Main cause of death (check one):
❑ Relapse or Progression
  Transplantation-related causes:
❑ Rejection/Poor graft function
❑ Pulmonary toxicity
❑ Infection
❑ Posttransplant lymphoproliferative disorder
❑ GVHD
❑ Cardiac toxicity
❑ VOD
❑ Other:

❑ Other:
❑ Unknown

SECONDARY MALIGNANCY

Secondary malignancy or lymphoproliferative disorder?
❑ Yes ❑ No ❑ Unknown

If yes, date of diagnosis:

___ ___ ___ ___ - ___ ___ - ___ ___
YYYY   MM   DD

If no, date of latest assessment:

___ ___ ___ ___ - ___ ___ - ___ ___
YYYY   MM   DD
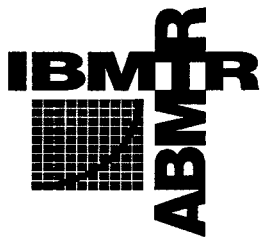
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Albany Medical Center	Albany	United States
New York Oncology Hematology, PC	Albany	United States
Presbyterian Health Care Services	Albuquerque	United States
Don & Sybil Harrington Cancer Center	Amarillo	United States
Oncology Associates	Anchorage	United States
University of Michigan Medical Center	Ann Arbor	United States
Gulhane Military Medical Academy	Ankara	Turkey
Arlington Cancer Center	Arlington	United States
Blood and Marrow Transplant Group of Georgia	Atlanta	United States
Emory Clinic	Atlanta	United States
Emory University - Egleston Children's Hospital	Atlanta	United States
Northside Hospital	Atlanta	United States
Southwest Regional Cancer Center	Austin	United States
Greater Baltimore Medical Center	Baltimore	United States
Johns Hopkins Oncology Center	Baltimore	United States
Sinai Hospital of Baltimore Cancer Institute	Baltimore	United States
University of Maryland Cancer Center	Baltimore	United States
Hosp. General Vall d'Hebron	Barcelona	Spain
Institut Catala d'Oncologia	Barcelona	Spain
Mary Bird Perkins Cancer Center	Baton Rouge	United States
Our Lady of the Lake Regional Cancer Center	Baton Rouge	United States
Alta Bates Hospital	Berkeley	United States
University of Alabama at Birmingham	Birmingham	United States
St. Luke's RMC/Mountain State Tumor Institute	Boise	United States
Dana-Farber Cancer Institute	Boston	United States
Montefiore Medical Center	Bronx	United States
Alexander Fleming Institute	Buenos Aires	Argentina
Centro de Internacion e Investigation	Buenos Aires	Argentina
Hospital Privado de Oncologia	Buenos Aires	Argentina
ITMO Fundacion Mainetti	Buenos Aires	Argentina
Navy Hospital "Pedro Mallo"	Buenos Aires	Argentina
Roswell Park Cancer Institute	Buffalo	United States
Lahey Hitchcock Clinic	Burlington	United States
Alberta Children's Hospital	Calgary	Canada
University of Calgary	Calgary	Canada
Royal Prince Alfred Hospital	Camperdown	Australia
Hemocentro UNICAMP	Campinas	Brazil
The Wynberg Hospital	Cape Town	South Africa
University of North Carolina Chapel Hill	Chapel Hill	United States
Medical University of South Carolina	Charleston	United States
Roper Care Alliance	Charleston	United States
Presbyterian Hospital Cancer Center	Charlotte	United States
Children's Memorial Hospital	Chicago	United States
Columbia Michael Reese Hospital	Chicago	United States

Institutions participating in the ABMTR, *continued.*

Mount Sinai Hospital Medical Center	Chicago	United States
Northwestern Memorial Hospital	Chicago	United States
Rush Presbyterian/St. Luke's Medical Center	Chicago	United States
University of Chicago Medical Center	Chicago	United States
University of Illinois	Chicago	United States
Children's Hospital Medical Center	Cincinnati	United States
Jewish Hospital of Cincinnati	Cincinnati	United States
Case Western Reserve University Hospital	Cleveland	United States
Cleveland Clinic Foundation	Cleveland	United States
Rainbow Babies & Children's Hospital	Cleveland	United States
Rocky Mountain Cancer Center	Colorado Springs	United States
University of South Carolina	Columbia	United States
Columbus Children's Hospital	Columbus	United States
Ohio State University Hospital	Columbus	United States
Hospital Privado de Cordoba	Cordoba	Argentina
Hospital de Clinicas	Curitiba	Brazil
Hospital Nossa Senhora das Gracas	Curitiba	Brazil
Baylor University Medical Center	Dallas	United States
Children's Medical Center of Dallas	Dallas	United States
Medical City Dallas Hospital	Dallas	United States
Miami Valley Hospital	Dayton	United States
Halifax Medical Center	Daytona Beach	United States
Oakwood Hospital and Medical Center	Dearborn	United States
Presbyterian St. Luke's Hospital	Denver	United States
Iowa Health System	Des Moines	United States
Henry Ford Hospital	Detroit	United States
Wayne State University	Detroit	United States
City of Hope National Medical Center	Duarte	United States
Duke University Medical Center	Durham	United States
North Shore Hematology/Oncology Associates	East Setauket	United States
Northwest Oncology & Hematology Associates	Elk Grove Village	United States
Fairfax Hospital	Falls Church	United States
University of Connecticut Health Center	Farmington	United States
Bone Marrow & Stem Cell Institute of Florida	Fort Lauderdale	United States
Cook-Fort Worth Children's Medical Center	Fort Worth	United States
Harris Methodist Oncology Program	Fort Worth	United States
University of Florida, Shands Hospital	Gainesville	United States
Cancer Center of the Carolinas	Greenville	United States
Hackensack Medical Center	Hackensack	United States
Queen Elizabeth II Health Sciences Center	Halifax	Canada
Institute de Hematologia e Immunologia	Havana	Cuba
Penn State Geisinger Health Systems	Hershey	United States
Hinsdale Hematology-Oncology Associates	Hinsdale	United States
Queen's Medical Center	Honolulu	United States
St. Francis Medical Center	Honolulu	United States
Baylor College of Medicine	Houston	United States
M.D. Anderson Cancer Center	Houston	United States
Indiana University Hospital & Outpatient Ctr.	Indianapolis	United States
Methodist Hospital of Indiana	Indianapolis	United States
Oncology/Hematology Associates	Indianapolis	United States
St. Vincent Hospital & Health Care Ctr.	Indianapolis	United States

Institutions participating in the ABMTR, *continued.*

Baptist Regional Cancer Center	Jacksonville	United States
Mayo Clinic Jacksonville	Jacksonville	United States
Nemours Children's Clinic/Wolfson Children's Hospital	Jacksonville	United States
University Medical Center	Jacksonville	United States
Children's Mercy Hospital	Kansas City	United States
Oncology/Hematology Associates of Kansas City	Kansas City	United States
University of Kansas Medical Center	Kansas City	United States
Thompson Cancer Survival Center	Knoxville	United States
Scripps Clinic & Research Foundation	La Jolla	United States
Dartmouth-Hitchcock Medical Center	Lebanon	United States
University of Kentucky Medical Center	Lexington	United States
Arkansas Cancer Research Center	Little Rock	United States
Saint Barnabas Medical Center	Livingston	United States
London Health Sciences Centre	London, Ontario	Canada
Kaiser Permanente of Southern California	Los Angeles	United States
UCLA Center for Health Sciences	Los Angeles	United States
USC/Norris Cancer Hospital	Los Angeles	United States
James Graham Brown Cancer Center	Louisville	United States
University of Wisconsin	Madison	United States
Hospital G.U. Gregorio Maranon	Madrid	Spain
North Shore University Hospital	Manhasset	United States
Marshfield Clinic	Marshfield	United States
Loyola University Medical Center	Maywood	United States
Methodist Hospital Central	Memphis	United States
Response Technologies	Memphis	United States
St. Jude Children's Research Hospital	Memphis	United States
Baptist Hospital of Miami	Miami	United States
Miami Children's Hospital	Miami	United States
University of Miami School of Medicine	Miami	United States
Froedtert Memorial Lutheran Hospital Cancer Center	Milwaukee	United States
Oncology of Wisconsin	Milwaukee	United States
St. Luke's Medical Center	Milwaukee	United States
Abbott Northwestern Hospital	Minneapolis	United States
University of Minnesota	Minneapolis	United States
Missoula Oncology & Infectious Disease	Missoula	United States
British Hospital & Faculty of Medicine	Montevideo	Uruguay
Hosp. Naciel Ministere of Public Health	Montevideo	Uruguay
IMPASA - Centro de Transplante de Medula Osea	Montevideo	Uruguay
Hôpital Ste. Justine	Montreal	Canada
Jewish General Hospital	Montreal	Canada
Montreal Children's Hospital	Montreal	Canada
Royal Victoria Hospital	Montreal	Canada
Sacre Coeur Hospital	Montreal	Canada
West Virginia University	Morgantown	United States
Vanderbilt University Medical Center	Nashville	United States
All India Institute of Medical Sciences	New Delhi	India
Louisiana State University Medical Center	New Orleans	United States
Memorial Medical Center	New Orleans	United States
Tulane University Medical Center	New Orleans	United States
Columbia University	New York	United States
Memorial Sloan-Kettering Cancer Center	New York	United States

Institutions participating in the ABMTR, *continued.*

Mt. Sinai Medical Center	New York	United States
New York Hospital Cornell Medical Center	New York	United States
New York University Medical Center	New York	United States
Medical Center of Delaware	Newark	United States
Hoag Cancer Center	Newport Beach	United States
Virginia Hematology/Oncology Associates	Newport News	United States
Virginia Oncology Associates	Norfolk	United States
Cancer Care Associates of Oklahoma City	Oklahoma City	United States
University of Oklahoma Health Sciences	Oklahoma City	United States
Immanuel Cancer Center	Omaha	United States
University of Nebraska Medical Center	Omaha	United States
Children's Hospital of Orange County	Orange	United States
Saint Joseph Hospital	Orange	United States
UCI Medical Center	Orange	United States
Walt Disney Memorial Cancer Institute	Orlando	United States
Ottawa General Hospital	Ottawa	Canada
The Desert Hospital Comprehensive Cancer Center	Palm Springs	United States
Clinica Univ. de Navarra	Pamplona	Spain
Lutheran General Hospital	Park Ridge	United States
Hematology Associates	Peoria	United States
Children's Hospital of Philadelphia	Philadelphia	United States
Hahnemann University Hospital	Philadelphia	United States
St. Christopher's Hospital for Children	Philadelphia	United States
Temple Univ. Comprehensive Cancer Center	Philadelphia	United States
Thomas Jefferson University Hospital	Philadelphia	United States
University of Pennsylvania Hospital	Philadelphia	United States
Children's Hospital of Pittsburgh	Pittsburgh	United States
Shadyside Hospital	Pittsburgh	United States
University of Pittsburgh	Pittsburgh	United States
Western Pennsylvania Hospital	Pittsburgh	United States
Legacy Good Samaritan Hospital	Portland	United States
Oregon Health Sciences Univ.	Portland	United States
Providence Portland Medical Center	Portland	United States
Instituto Portugues de Oncologia - Centro do Porto	Porto	Portugal
Alfred Hospital	Prahran	Australia
Roger Williams Medical Center	Providence	United States
Centro de Hematologia y Medicina Interna	Puebla	Mexico
Univ. of Puerto Rico School of Medicine	Puerto Rico	United States
Hôpital du Saint-Sacrement	Quebec City	Canada
Cancer & Blood Institute of the Desert	Rancho Mirage	United States
Riverview Medical Center	Red Bank	United States
Washow Regional Cancer Center	Reno	United States
Medical College of Virginia	Richmond	United States
Univ. Federal de Rio de Janeiro	Rio de Janeiro	Brazil
Mayo Clinic Rochester	Rochester	United States
University of Rochester	Rochester	United States
Universita Cattolica Sacro Cuore	Rome	Italy
Sutter Memorial Hospital	Sacramento	United States
Univ. of California Davis Cancer Center	Sacramento	United States
Cardinal Glennon Children's Hospital	St. Louis	United States
St. Louis Children's Hospital	St. Louis	United States

Institutions participating in the ABMTR, *continued.*

St. Louis University Medical Center	St. Louis	United States
Washington University School of Medicine	St. Louis	United States
Methodist Hospital/Nicollet Cancer Center	St. Louis Park	United States
All Children's Hospital	St. Petersburg	United States
Petrov Res. Inst. of Oncology	St. Petersburg	Russia
LDS Hospital	Salt Lake City	United States
University of Utah Medical Center	Salt Lake City	United States
Santa Rosa Children's Hospital	San Antonio	United States
South Texas Cancer Institute	San Antonio	United States
University of Texas Health Sciences Ctr.	San Antonio	United States
Children's Hospital San Diego	San Diego	United States
University of CA, San Diego	San Diego	United States
Inst. Nacional de Cancerologia	San Fernando	Mexico
University of CA, San Francisco Medical Ctr.	San Francisco	United States
University of California, San Francisco, Pediatrics	San Francisco	United States
Hosp. Especialidades Centro Medico	San Mateo	Mexico
Hospital do Cancer	Sao Paulo	Brazil
Mayo Clinic Scottsdale	Scottsdale	United States
LSU Medical Center-Shreveport	Shreveport	United States
Avera Cancer Institute	Sioux Falls	United States
Spartanburg Regional Medical Center	Spartanburg	United States
Baystate Medical Center	Springfield	United States
St. John's Regional Health Center	Springfield	United States
Bennett Cancer Center	Stamford	United States
Stanford University Hospital	Stanford	United States
State University of New York at Stone Brook	Stony Brook	United States
Northeastern Ontario Regional Cancer Centre	Sudbury	Canada
State University of New York Health Science Center	Syracuse	United States
H. Lee Moffitt Cancer Center	Tampa	United States
Scott & White Clinic	Temple	United States
St. Vincent Mercy Medical Center	Toledo	United States
Hospital for Sick Children	Toronto	Canada
The Toronto Hospital	Toronto	Canada
Arizona Cancer Center	Tucson	United States
Arizona Oncology Associates	Tucson	United States
St. Francis Hospital	Tulsa	United States
New York Medical College	Valhalla	United States
British Columbia's Children's Hospital	Vancouver	Canada
Vancouver General Hospital	Vancouver	Canada
Donauspital	Vienna	Austria
John Muir Medical Center	Walnut Creek	United States
Georgetown University Medical Center	Washington, DC	United States
George Washington University Medical Ctr.	Washington, DC	United States
Walter Reed Army Medical Center	Washington, DC	United States
Washington Cancer Institute	Washington, DC	United States
Waukesha Memorial Regional Cancer Center	Waukesha	United States
Good Samaritan Medical Center/Duke University	West Palm Beach	United States
St. Francis Hospital	Wichita	United States
Manitoba Cancer Treatment Center	Winnipeg	Canada
Piedmont Hematology/Oncology Associates	Winston-Salem	United States

Institutions participating in the ABMTR, *continued.*

Wake Forest University	Winston-Salem	United States
University of Massachusetts Medical Center	Worcester	United States
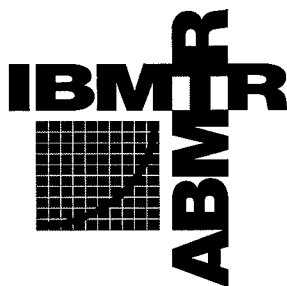
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ABMTR Statistician: J. Douglas Rizzo, MD

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Robert F. Taylor	St. Luke's Medical Center, Milwaukee, WI
L. Bik To	Hanson Centre for Cancer Research, Adelaide, South Aust, AUSTRALIA
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John R. Wingard	University of Florida, Gainesville, FL
Jane N. Winter	Northwestern University Hospital, Chicago, IL
Steven N. Wolff	Vanderbilt University Medical Center, Nashville, TN

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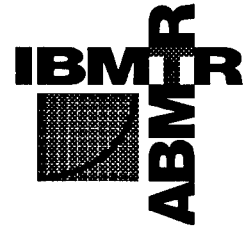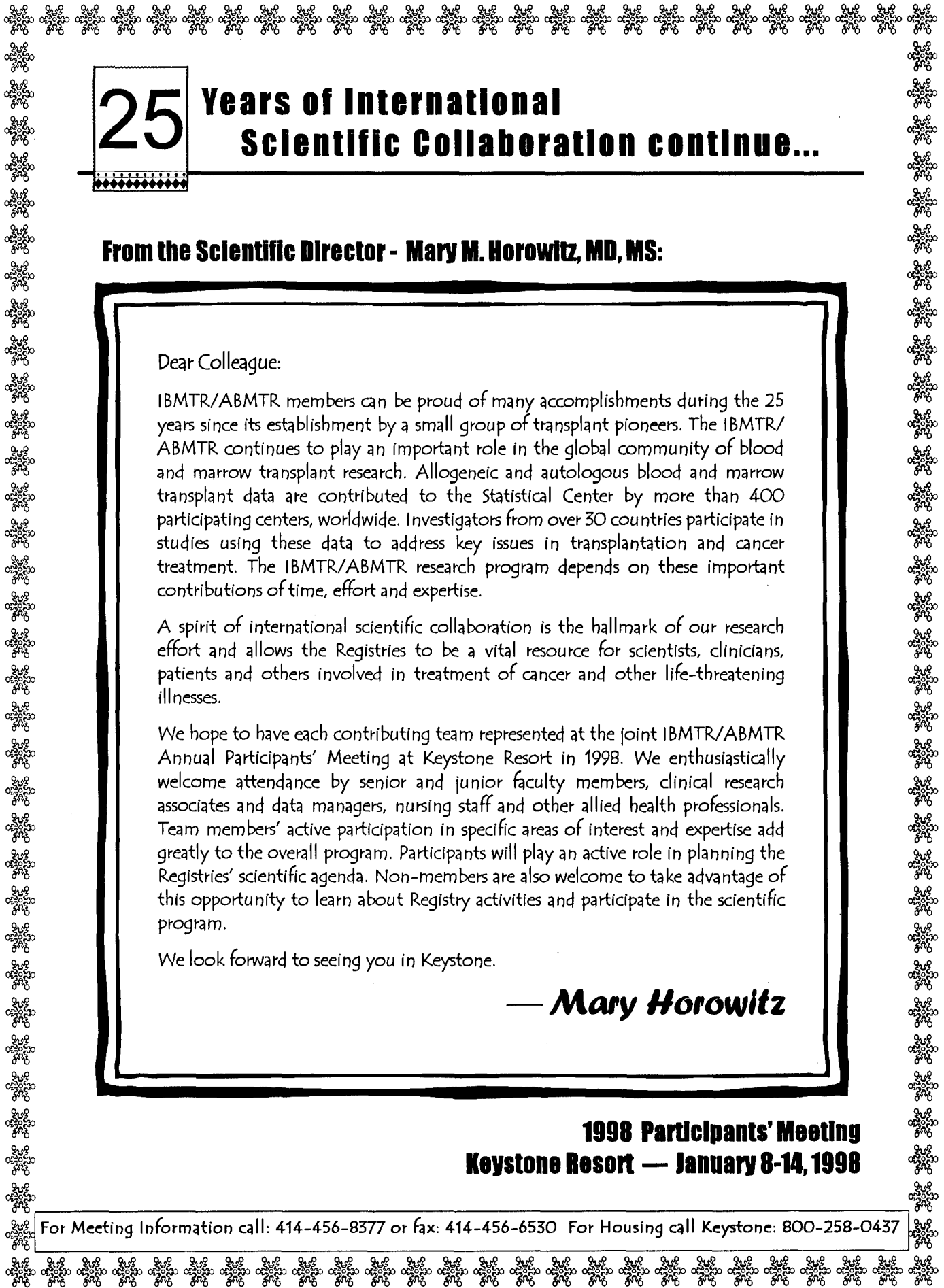
1998 Participants' Meeting

Keystone Resort, Colorado
January 8 - 14, 1998

MEDICAL COLLEGE OF WISCONSIN

CME *program*

25 Years of International Scientific Collaboration continue...

From the Scientific Director - Mary M. Horowitz, MD, MS:

Dear Colleague:

IBMTR/ABMTR members can be proud of many accomplishments during the 25 years since its establishment by a small group of transplant pioneers. The IBMTR/ABMTR continues to play an important role in the global community of blood and marrow transplant research. Allogeneic and autologous blood and marrow transplant data are contributed to the Statistical Center by more than 400 participating centers, worldwide. Investigators from over 30 countries participate in studies using these data to address key issues in transplantation and cancer treatment. The IBMTR/ABMTR research program depends on these important contributions of time, effort and expertise.

A spirit of international scientific collaboration is the hallmark of our research effort and allows the Registries to be a vital resource for scientists, clinicians, patients and others involved in treatment of cancer and other life-threatening illnesses.

We hope to have each contributing team represented at the joint IBMTR/ABMTR Annual Participants' Meeting at Keystone Resort in 1998. We enthusiastically welcome attendance by senior and junior faculty members, clinical research associates and data managers, nursing staff and other allied health professionals. Team members' active participation in specific areas of interest and expertise add greatly to the overall program. Participants will play an active role in planning the Registries' scientific agenda. Non-members are also welcome to take advantage of this opportunity to learn about Registry activities and participate in the scientific program.

We look forward to seeing you in Keystone.

— *Mary Horowitz*

1998 Participants' Meeting
Keystone Resort — January 8-14, 1998

For Meeting Information call: 414-456-8377 or fax: 414-456-6530 For Housing call Keystone: 800-258-0437

Why you should attend the 1998 Participants' Meeting

Meeting Objectives

♦ to report on the "state of the art" in blood and marrow transplantation;

♦ to review Registry accomplishments;

♦ to discuss the progress of current and ongoing scientific studies;

♦ to set the Registries' scientific agenda for the next year;

♦ to provide training in data management and analysis for data managers, nurses and other allied health professionals working in blood and marrow transplantation.

Working Committee Meetings

IBMTR and ABMTR disease- and treatment-specific Working Committees are open to all interested in taking an ACTIVE role in ongoing and future studies. All Working Committee members should plan to attend.

Working Committees will review the past year's accomplishments, discuss current studies and plan future studies. Priorities for proposed studies will be established. Participation in these meetings is an opportunity to help determine the Registries' scientific agenda.

1998 IBMTR & ABMTR Working Committees

Committee		Chairs
IBMTR/ABMTR Acute Leukemia	chairs:	Daniel Weisdorf -IBMTR
		Armand Keating -ABMTR
ABMTR Breast Cancer	chair:	Karen Antman
IBMTR/ABMTR CLL	chairs:	Emilio Montserrat -IBMTR
(Chronic Lymphocytic Leukemia)		Richard Champlin -ABMTR
IBMTR Chronic Myelogenous Leukemia	chair:	Phil McGlave
IBMTR GVH/GVL and Immune	chairs:	A John Barrett
Reconstitution		Olle Ringden
IBMTR Histocompatibility,	chair:	Richard Champlin
Alternative Donors & Stem Cell Sources		
IBMTR Immune Deficiencies	chair:	Alexandra Filipovich
& Metabolic Diseases		
IBMTR Late Effects	chair:	Gérard Socié
IBMTR/ABMTR Lymphoma	chairs:	Koen Van Besien -IBMTR
		Hillard Lazarus, Julie Vose -ABMTR
ABMTR Multiple Myeloma	chair:	Sundar Jagannath
IBMTR/ABMTR Pediatric Cancer	chair:	Bruce Camitta
IBMTR Severe Aplastic Anemia	chair:	Jill Hows
IBMTR/ABMTR Solid Tumors	chair:	Patrick Stiff

Registration Information

Complete the enclosed Registration Form, including your VISA or MasterCard number, and fax to the Statistical Center at 414-456-6530. Checks, made payable to "The Medical College of Wisconsin - IBMTR", may be mailed to the Statistical Center. We regret that we cannot accept American Express for meeting registration fees. International funds must be submitted in US Dollars. All credit cards are processed in US Dollars and are subject to current exchange rates.

Registration Forms received prior to November 1 qualify for a preregistration discount. Those received on or after December 1 must pay the full conference rate, as indicated. Payment is due with the Registration Form.

Registration fees include admission to all sessions and exhibits, all IBMTR/ABMTR conference materials, abstract book and program, breakfast, coffee breaks and refreshments, and evening poster session receptions. Confirmation for each registered participant will be returned by fax.

1997 IBMTR/ABMTR MEETING REGISTRATION FEES

	before Nov 1	before Dec 1	on or after Dec 1
PARTICIPATING TEAM MEMBERS			
◆ MD/PhD	$395	$475	$550
◆ Allied Health Professionals*	$100	$125	$145
◆ Accompanying Persons	$150	$200	$250
CORPORATE MEMBERS	$400	$500	$600
NON-MEMBERS	$575	$675	$775

*Data Management Grants: A limited number of $500 grants are available on a first-come, first-serve basis to data management personnel attending the Data Management Workshops. To be eligible, data managers must be from centers currently reporting, or planning to report, autotransplants for breast cancer. The enclosed application must be returned to the Statistical Center prior to November 1, 1997 for consideration. See application for additional details. For more information contact D'Etta Waldoch Severson, CMP, Associate Director-International Programs at the Statistical Center at: 414-456-8377.

Conference Registration Cancellation: Meeting registration is fully refundable until November 30. All cancellations must be made in writing and may be faxed to the Statistical Center at 414-456-6530. Cancellations made on or after December 1 will be assessed a non-refundable handling fee of US $50; On January 1 the cancellation fee will increase to US $75. "No shows" without written notification will be assessed the full prepaid registration fee with no refund provision.

1998 Participants' Meeting
Keystone Resort — January 8-14

For Meeting Information call: 414-456-8377 or fax: 414-456-6530 For Housing call Keystone: 800-258-0437

ousing & Accommodations

Call or Fax Today for Reservations   Housing Form Due: December 1

A limited number of guest rooms and condominiums at special conference rates are reserved for IBMTR/ABMTR Meeting participants. The rates are available for 3 days before and after the conference for those wishing to extend their stay in Colorado's picturesque Arapahoe region. Take advantage of these special room rates, which represent substantial discounts during peak season for Keystone-area resorts.

Please complete the enclosed Housing Form and return it directly to Keystone Resort prior to December 1, 1997. It is strongly recommended that reservations be made early, as accommodations will be difficult and more costly to obtain after the deadline. Please indicate a major credit card number for the first and last night's deposit and applicable taxes. Reservations will not be held without a deposit. Reservations made after the deadline may not be available at the discounted conference rate and last minute requests may be impossible to accommodate (see Housing Form for more information).

1998 KEYSTONE RESORT ROOM RATES — Subject to Availability

Keystone Lodge:	$162/night single occupancy	$177/night double
Inn at Keystone:	$126/night single occupancy	$141/night double
Village Studio:	$163/night single or double	
Village 1 Bedroom:	$178/night single or double	
Village 2 Bedroom:	$262/single, double, triple or quad	
Resort Studio:	$146/night single or double	
Resort 1 Bedroom:	$168/night single or double	
Mountain Studio:	$183/night single or double	

For Meeting Information call: 414-456-8377 or fax: 414-456-6530   For Housing call Keystone: 800-258-0437

Data Management Workshops

Featuring 2 Learning Tracks...   Friday, January 9, 1998

Due to enthusiastic feedback from participating IBMTR and ABMTR data management professionals, we are pleased to offer a full day of Data Management Workshops at the 1998 Participants' Meeting. Data managers, clinical research associates and research nurses will find topics of interest and opportunities for direct communication with on-site Statistical Center staff members leading informal, participatory Workshops on two tracks. Both tracks will discuss recent changes in IBMTR/ABMTR Registration and Reporting procedures.

> **TRACK I**   fundamental concepts for those attending the Workshops for the first time.
>
> **TRACK II**   designed for experienced data management and nursing professionals;
>   features special topics related to clinical research and audit management.

Additionally, StemCell Technologies Inc will demonstrate StemSoft software and their interrelated statistical analysis package. "Hands-on" training is available for those who preregister with StemCell Technologies Inc (details below). Data management personnel are invited to stay for the entire meeting.

$500 Grants for Data Management Workshops

The Statistical Center was awarded a grant from the US Department of Defense which will provide 30 data managers with $500 each to offset some of the travel costs associated with attending the Workshops. To be eligible, data managers must be from centers currently reporting, or planning to report autotransplants for breast cancer.

Grants are awarded as they are received, with priority given to first-time attendees. Please complete the enclosed Grant Application Form and return it by fax with your completed Registration Form as soon as possible. The deadline for Grant Application submission is November 1, 1997.

<center>*Grant awards go fast — do not delay!*</center>

StemCell Technologies Inc

StemCell Technologies Inc will offer full-day hands-on training sessions for their StemSoft line of products on Saturday - January 10, Sunday - January 11 and Monday - January 12. Training sessions will be limited to 20 participants each, on a first-come, first-serve basis, and are subject to cancellation if less than half full.

Data Managers and all 'end-users' of StemSoft software who want to achieve greater levels of performance and effectiveness with the software will benefit. The fee for participating in each session is $400. Please contact Ellen Low at StemCell Technologies Inc in Vancouver, British Columbia (Canada) at 800-667-0322 or 604-877-0713, or stemsoft@stemcell.com.

For Meeting Information call: 414-456-8377 or fax: 414-456-6530   For Housing call Keystone: 800-258-0437

More about Data Management

General Sessions

Introduction   **Barbara McGary, Manager of Information Systems, IBMTR/ABMTR**
Discuss Workshop format and dispell myths.

Scoring Common Toxicities   **Phil Rowlings, MD, Assistant Scientific Director, IBMTR/ABMTR**
Useful information for scoring common toxicities (GVHD, VOD) on IBMTR/ABMTR Report Forms.

Overview of Statistics   **Judith Veum Stone, Biostatistician, IBMTR/ABMTR**
What does the Statistical Center do with all those data? Discussion of outcome variables, in's and out's of working with the databases and basics of statistical analyses.

High-Dose Therapies   **Kathleen Kovatovic, RPh - Clinical Oncology & BMT Pharmacist**
                                                Froedtert Memorial Lutheran Hospital, Milwaukee
How high-dose drug therapy in BMT differs from other disciplines.

Update on StemSoft   **David Reeves - Sr Programmer/Analyst, StemCell Technologies Inc., Vancouver, BC**
Quick demonstration on newest products available from StemCell Technologies. Opportunity to ask questions and sign up for full-day training seminars (see page 6 for details).

Two Learning Tracks...

TRACK I: First Timers

Registration & Reporting: Why Both?   **Barbara McGary, Manager of Information Systems, IBMTR/ABMTR**
Valuable information for first-timers regarding IBMTR/ABMTR registration and reporting procedures; why it is necessary to complete both registration and reporting forms and stay up-to-date.

Hands-on Registration 101   **Sharon Nell, Communications Coordinator, IBMTR/ABMTR**
How to complete IBMTR/ABMTR *Registration* Forms from A-Z; helpful for those just getting started, or with questions on Registration procedures; question & answer session will follow.

Hands-on Reporting 101   **Diane Knutson, Systems Coordinator, IBMTR/ABMTR**
Completing IBMTR/ABMTR *Reporting* Forms is not as difficult as it may first appear; obtain useful information to get started; opportunity to address specific questions on Reporting procedures.

TRACK II: For those who have attended IBMTR/ABMTR Workshops previously

Practical Aspects of Reporting: An Update   **Diane Knutson, Systems Coordinator, IBMTR/ABMTR**
For those who have heard Diane present "Hands-on Reporting 101"; an update on working with IBMTR/ABMTR *Reporting* Forms; practical tips and suggestions for time-saving measures.

Registry Audit Survival Tactics   **Claudia Kabler-Babbitt, BSA, CCRC - Sr. Clinical Studies Coordinator**
                                   Bone Marrow Transplant Program, Medical College of Wisconsin, Milwaukee
Ever wonder what an IBMTR/ABMTR Audit is like? Take it from Claudia! Practical tips for gathering data on a daily basis that will make audit day run like clockwork and sigh a gigantic breath of relief!

For Meeting Information call: 414-456-8377 or fax: 414-456-6530   For Housing call Keystone: 800-258-0437

Poster Sessions

Poster Sessions Combined with Evening Receptions

The late afternoon poster session on Monday, January 12 will be combined with a hosted reception featuring Keystone Resort's award-winning light buffet-style cuisine and beverages.

A $500 investigator award will be given for the best abstract submitted, as determined by IBMTR/ABMTR Committee Chairs.

Abstract Instructions Submission Deadline: November 15, 1997

1. Abstract must be typed on the enclosed ABSTRACT FORM.

2. CAPITALIZE entire title and UNDERSCORE author's names (underscoring or capitalizing for emphasis in text is unacceptable. Single space all typing (no space between title and body or between paragraphs). Indent each paragraph three spaces. Do not indent title. Draw special symbols in black ink.

3. Please do not reduce the abstract on a photocopy machine! Type abstract in 12 point type or larger. Abstracts submitted in a reduced format may not be included in the Abstract Book. Abstracts must be received by November 15, 1997 to ensure publication in the Abstract Book. ABSTRACT WILL APPEAR EXACTLY AS SUBMITTED. Smudges, errors, misspellings, faint type, etc. should be avoided.

4. Make the TITLE brief, clearly indicating the nature of the investigation. After the title, list the authors' names and institutional affiliations. Omit degrees, titles, institutional appointments, street addresses and zip or postal code.

5. Organize the body of the abstract as follows:

    • A statement of the purpose of the study (preferably one sentence)
    • A statement of the methods used
    • A summary of the results presented in sufficient detail to support the conclusions
    • A statement of conclusions reached. It is not satisfactory to state, "The results will be discussed" or "Other data will be presented.

6. Simple tables or graphs, neat and in black ink, may be included if they fit within the Abstract Form.

7. Abbreviations must be defined by placing them in parentheses after the full word the first time they appear. Use numerals to indicate numbers except when beginning sentences.

8. The material must be in camera-ready form, i.e., type must be laser quality, 300 dpi or better (no dot matrix). USE BLACK INK. Practice fitting text into the Abstract Form.

9. NO abstract may be presented if previously presented orally at a national or international meeting.

10. Submit abstract (original plus 2 copies) BEFORE NOVEMBER 15, 1997.

Continuing Medical Education

The Medical College of Wisconsin (MCW) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. MCW designates this continuing medical education (CME) activity for 23.5 credit hours in Category I of the Physician's Recognition Award of the American Medical Association. Each physician should claim only those hours of credit that he/she actually spent in the educational activity. MCW also designates this activity for 23.5 contact hours of continuing education for allied health professionals. Participants requesting credit should check the appropriate box on the enclosed Registration Form and must include social security number. A separate form will be available at the conference to designate actual hours attended which will be required for credit to be administered.

Disclosure

The Statistical Center of the IBMTR/ABMTR is committed to providing unbiased, balanced and objective educational and scientific programs. In accordance with ACCME guidelines, all 1998 Annual Meeting speakers are asked to provide relevant disclosure statements. Disclosures are on file at the Medical College of Wisconsin Continuing Medical Education office and will be available on-site at the Registration Desk for review.

Travel Assistance

CAUTION: Weather at the Denver airport is not a good indication of driving conditions in the mountains. Before heading west on I-70, check the local forecast and road conditions. Those not familiar with driving in winter conditions should consider using Resort Express shuttle service.

Hertz - the official car rental company

Hertz has been appointed the official car rental company for the 1998 IBMTR/ABMTR Participants' Meeting in Keystone. Special discount rates, with free unlimited mileage are guaranteed one week before and one week after the IBMTR/ABMTR meeting dates, subject to car availability. At the time of reservation booking, these rates will automatically be compared to Hertz published rates, assuring meeting participants are quoted the best comparable rates available at Denver International Airport. Standard rental conditions and qualifications apply, including minimum rental age. Check with your Hertz representative for further details.

> For reservations, call Hertz at 1-800-654-2240 in the US, in Canada at 1-800-263-0600, or check with your travel agent. Refer to CV# 42539.

Resort Express

Regularly scheduled shuttle service will meet you at the baggage claim level (level 5) at the Denver International Airport and deliver you to Keystone Lodge, with 16 daily departures. Mention the IBMTR/ABMTR Meeting at Keystone for discounted group fares: $70 per person round trip; $35 per person one way; $285 for 10 passenger vans one way; $395 for 6 passenger limosine one way.

> For reservations, call Resort Express at 800-334-7433 or 970-468-7600

For Meeting Information call: 414-456-8377 or fax: 414-456-6530   For Housing call Keystone: 800-258-0437

Questions About the Conference, Support/Exhibit Opportunities

For general questions about the Annual Participants' Meeting please contact:

D'Etta Waldoch Severson, CMP
Associate Director-International Programs
IBMTR/ABMTR Statistical Center
414-456-8377
fax: 414-456-6530

Corporations and others interested in meeting support and exhibit opportunities may contact:

Susan U. Ladwig, MA
Associate Director of Development
IBMTR/ABMTR Statistical Center
c/o Medical College of Wisconsin
8701 Watertown Plank Road
Milwaukee, WI, 53226, USA
414-456-8325
fax: 414-456-6530

MEDICAL COLLEGE OF WISCONSIN

CME *program*

1998 Participants' Meeting
January 8-14
Keystone Resort, Colorado, USA

For Meeting Information call: 414-456-8377 or fax: 414-456-6530 For Housing call Keystone: 800-258-0437

1998 IBMTR/ABMTR Participants' Meeting

Keystone Resort, Colorado

January 8 - 14, 1998

High Altitude Warning:

Keystone Resort is located 9,300 feet above sea level. If you have any health problems which may be complicated by high altitude, please consult with your physician before registering for the IBMTR/ABMTR Meeting.

NOTES:

1998 IBMTR/ABMTR Participants' Meeting

Keystone Resort, Colorado

January 8 - 14, 1998

Supported by unrestricted educational grants from:

- ✳ Aastrom Biosciences
- ✳ Amgen, Inc.
- ✳ Baxter Biotech Group, North America
- ✳ BioChem Pharma
- ✳ BIS Laboratories
- ✳ Bristol-Myers Squibb Oncology
- ✳ Cell Therapeutics, Inc.
- ✳ CellPro, Inc.
- ✳ Centeon
- ✳ Chiron Therapeutics
- ✳ COBE BCT
- ✳ Fujisawa USA
- ✳ Immunex Corporation
- ✳ ISHAGE
- ✳ The Liposome Company, Inc.
- ✳ Medical SafeTec
- ✳ NeXstar Pharmaceuticals, Inc.
- ✳ Novartis Pharmaceuticals
- ✳ OrthoBiotech, Inc.
- ✳ Pfizer, Inc.
- ✳ Pharmacia and Upjohn Company
- ✳ Roche Laboratories
- ✳ SangStat Medical Corporation
- ✳ Schering-Plough Corporation
- ✳ Searle
- ✳ SEQUUS Pharmaceuticals
- ✳ StemCell Technologies Inc
- ✳ SyStemix
- ✳ Therakos
- ✳ Wyeth-Ayerst Laboratories

DATA MANAGEMENT WORKSHOP PROGRAM EVALUATION
Keystone, CO   January 8-14, 1998
(Rating Scale: 1-poor 2-fair 3-good 4-very good 5-excellent)

Keystone Resort
| 1) 2% | 2) 0% | 3) 19% | 4) 27% | 5) 52% |

Overall Program
| 1) 0% | 2) 5% | 3) 25% | 4) 50% | 5) 20% |

Topics
| 1) 0% | 2) 4% | 3) 31% | 4) 40% | 5) 25% |

Audio Visual
| 1) 4% | 2) 12% | 3) 35% | 4) 25% | 5) 24% |

Handouts
| 1) 2% | 2) 13% | 3) 34% | 4) 28% | 5) 23% |

Meeting Room
| 1) 2% | 2) 4% | 3) 34% | 4) 26% | 5) 34% |

Food & Beverage
| 1) 0% | 2) 2% | 3) 20% | 4) 29% | 5) 49% |

Speakers (Overall)
| 1) 0% | 2) 7% | 3) 33% | 4) 40% | 5) 20% |

LeeAnn Baxter-Lowe
| 1) 0% | 2) 12% | 3) 27% | 4) 34% | 5) 27% |

Claudia Kabler-Babbitt
| 1) 8% | 2) 11% | 3) 33% | 4) 33% | 5) 15% |

Armand Keating for Carolyn Keever Taylor
| 1) 0% | 2) 3% | 3) 16% | 4) 32% | 5) 49% |

Diane Knutson
| 1) 0% | 2) 3% | 3) 18% | 4) 30% | 5) 49% |

Kathleen Kovatovic
| 1) 0% | 2) 16% | 3) 35% | 4) 33% | 5) 16% |

Barbara McGary
1) 2%   2) 11%   3) 39%   4) 37%   5) 11%

Sandy Murphy
1) 0%   2) 8%   3) 36%   4) 43%   5) 13%

Sharon Nell
1) 0%   2) 4%   3) 12%   4) 56%   5) 28%

Jakob Passweg
1) 0%   2) 0%   3) 20%   4) 50%   5) 30%

David Reeves
1) 0%   2) 9%   3) 46%   4) 26%   5) 19%

Meeting Participants
1) 3%   2) 7%   3) 29%   4) 32%   5) 29%

Attention
1) 0%   2) 11%   3) 31%   4) 33%   5) 25%

Enthusiasm
1) 0%   2) 16%   3) 31%   4) 31%   5) 22%

Involvement in Discussion
1) 2%   2) 19%   3) 38%   4) 26%   5) 15%

1998 DATA MANAGEMENT SESSION GRANTEES

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"Data Management 101"
'Embassy Suites Hotel, Milwaukee
November 1-3, 1998

Arrivals   **Saturday October 31** ───────────

♦ Attendees arriving early for that Saturday-night stay (to appreciate lower airline fares) may enjoy the day relaxing around the pool at Embassy Suites Hotel or shopping at nearby Brookfield Square Shopping Center or Loehmann's Plaza on Bluemound Road, or any number of other activities in the Milwaukee area.

Day One   **Sunday November 1** ───────────

♦ Enjoy cooked-to-order breakfast, compliments of Embassy Suites Hotel

8:00 am - 9:00 am	Registration	
9:00 am - 9:15 am	Welcome	Barbara McGary
9:15 am - 10:00 am	Basics of BMT	J. Douglas Rizzo, MD
10:00 am - 11:00 am	Registration Database/Forms	Barbara McGary
11:00 am - 11:15 am	break	
11:15 am - 11:30 am	StemSoft Product Demonstration	Jacki Hatfield
11:30 am - 12:30 pm	Core Forms 101	Diane Knutson
12:30 pm - 1:30 pm	luncheon	
1:30 pm - 3:00 pm	Core Forms 102	Diane Knutson
3:00 pm - 3:15 pm	break	
3:15 pm - 5:00 pm	Graft Inserts & Theory	Carolyn Taylor, PhD

♦ evening free—enjoy a complimentary cocktail reception at Embassy Suites 5:30-7:30 pm

Day Two   **Monday November 2** ───────────

♦ Enjoy cooked-to-order breakfast, compliments of Embassy Suites Hotel

8:00 am - 9:00 am	Registration	
9:00 am - 10:30 am	Disease-Specific Forms	Diane Knutson,
10:30 am - 10:45 am	break	
10:45 am - 12:00 noon	Disease-Specific Forms continued	Diane Knutson
12:00 noon - 1:15 pm	luncheon	

♦ Concurrent Afternoon Sessions

1:30 pm - 2:30 pm	Efficient Data Abstracting	Roundtable facilitators
2:30 pm - 3:00 pm	Audit Update	Kathy Kovatovic, RPh
3:00 pm - 3:15 pm	break	
3:15 pm - 5:00 pm	Basic Statistics	IBMTR Biostatisticians

StemSoft is offering the following sessions free of charge, facilitated by Jacki Hatfield and Geoff Brown:

1:30 pm - 3:00 pm	Managing Your Electronic Environment with *BMTbase*
3:00 pm - 3:15 pm	break
3:15 pm - 5:00 pm	Managing Your Electronic Environment with *BMTbase*

♦ evening free—enjoy a complimentary cocktail reception at Embassy Suites 5:30-7:30 pm

Day Three   **Tuesday November 3** ───────────

♦ Enjoy cooked-to-order breakfast, compliments of Embassy Suites Hotel

Tuesday sessions require $400 fee & preregistration; contact Jacki Hatfield at StemSoft in Vancouver: 602-668-0838.

8:00 am - 12:00 noon	BMTbase (095 Registration, 095 Reports, BMTmerge, BMTtransfer)
12:00 noon - 1:00 pm	luncheon sponsored by StemSoft
1:00 pm - 5:00 pm	*BMTstats*

♦ evening free—enjoy a complimentary cocktail reception at Embassy Suites 5:30-7:30 pm

F A S T   F A C T S

MEDICAL COLLEGE OF WISCONSIN

CME *program*

"Data Management 101"
A Workshop for First Time Attendees
Embassy Suites Hotel, Milwaukee, WI
November 1-3, 1998

IBMTR / ABMTR

EDUCATIONAL OBJECTIVES
* Provide training in data management and analysis for data managers, nurses and other allied health professionals in BMT
* Provide a forum for discussion of IBMTR/ABMTR guidelines for completing registration and reporting forms.
(refer to enclosed Provisional Agenda)

MEETING REGISTRATION
There is no charge for attending "Data Management 101" for Sunday and Monday sessions, if you register before October 9th. After October 9th, a $50 late fee will be assessed, payable in cash or by check at on-site registration. Please fax the Registration Form (below) to the Workshop Registration office: 414-827-4997. Call D'Etta at 414-456-8377 if you have questions.

There is a $400 fee for attending the StemSoft Workshop on Tuesday. Contact Jacki Hatfield at 602-668-0838 at StemSoft in Vancouver, BC (Canada) to register for Tuesday's sessions.

HOUSING
$99 singles
$109 doubles
Embassy Suites Hotel is located at 1200 South Moorland Road, Brookfield, Wisconsin, 53008-1463
The hotel offers two-room suites with galley kitchen and private bedroom. Each morning guests of Embassy Suites enjoy a complimentary cooked-to-order breakfast, and each evening complimentary cocktails are available at a two-hour reception.

Call Embassy Suites Reservations BEFORE OCTOBER 9th at: 800-444-6404, refer to "G1273"

ATTIRE
Casual and comfortable—temperatures in Milwaukee are variable in November, but mostly cool to cold.

ARRIVAL
Upon arrival at Milwaukee's General Mitchell International Airport, proceed to the baggage claim area #4 and use the house phone to call Embassy Suites to send the complimentary shuttle. Rental cars are also available in the same area. Alternatively, one-way cab fare from the Airport to Embassy Suites is approximately $30.

EDUCATION CREDITS
The Medical College of Wisconsin (MCW) is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. MCW designates this activity for up to 12 contact hours of continuing education for allied health professionals.

REGISTRATION FORM

FAX to Workshop Registration Office at: 414-827-4997
or mail to IBMTR/ABMTR, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI, 53226, USA

Name:_____

Title:_____

Institution:_____

Address:_____

City:_____ State/Province:_____ Country:_____

Zip/Postal Code:_____ Telephone:_____

FAX:_____ E-mail:_____

US Social Security/Canadian Social Insurance Number (required for education credits): __ __ __-__ __-__ __ __ __

IBMTR Team Number: __ __ __   ABMTR Team Number: __ __ __   Team Leader:_____

Anticipated arrival date: _____   Anticipated departure date:_____

Please indicate below which sessions you plan to attend (you are not obligated):

Sunday, November 1:   ☐ morning sessions   ☐ afternoon sessions

Monday, November 2:   ☐ morning sessions

  pm concurrent sessions: ☐ Data Abstracting   ☐ Audit Update   ☐ Basic Statistics

            ☐ Managing Your Electronic Environment With BMTbase (repeated twice)

Tuesday, November 3:   ☐ BMTbase   ☐ BMTstats   *($400 + preregistration required for these sessions; contact Jacki Hatfield at StemSoft-see above)*

Sorry — Travel Grants are not available for this program

"DATA MANAGEMENT 101"
PROGRAM EVALUATION SUMMARY

Embassy Suites Hotel, Milwaukee, WI * November 1-3, 1998

Embassy Suites Hotel
poor 0%   fair 10%   good 16%   very good 55%   excellent 19%

Hotel Comments:
-Excellent except exercize room too hot and need new equiptment.
-Better exersize equiptment
-In the middle of nowhere! Green velour couches?! Cracked tile... but helpful staff who would drive us around if we asked.
-Too warm in meeting rooms
-Had to change rooms 3 times. Had to check out 12:00 when conference wasn't over until 5:00. Was not aware of this until day of arrival

Overall Program
Poor 0%   fair 0%   good 7%   very good 60%   excellent 33%
Topics
Poor 0%   fair 0%   good 18%   very good 42%   excellent 40%
Audio-visuals
Poor 0%   fair 12%   good 18%   very good 45%   excellent 25%
Hand-outs
Poor 0%   fair 0%   good 7%   very good 52%   excellent 41%
Meeting Rooms
Poor 0%   fair 0%   good 9%   very good 59%   excellent 32%
Food & Beverage
Poor 0%   fair 3%   good 3%   very good 47%   excellent 47%

Overall Program Comments:
-You may wish to clump the clinical background and allow the clinicians to opt out of that particular portion.
-Very impressed, did not think it would be so informative & valuable to me.
-Notebook very helpful.
-Good folder. Noise from next door-too warm on first day-have break earlier 11:30 break/12:30 lunch too close.

Sessions (Overall)
Poor 0%   fair 0%   good 12%   very good 56%   excellent 32%
Basics of BMT
Poor 0%   fair 6%   good 21%   very good 29%   excellent 44%
Registration Database/Form
Poor 0%   fair 11%   good 21%   very good 24%   excellent 44%
Core Forms 101/102
Poor 0%   fair 0%   good 9%   very good 38%   excellent 53%
Graft Inserts & Theory
Poor 0%   fair 13%   good 27%   very good 37%   excellent 23%

Disease-Specific Forms
Poor 0%   fair 0%   good 6%   very good 42%   excellent 52%
Efficient Data Abstracting
Poor 0%   fair 10%   good 20%   very good 40%   excellent 30%
Audit Update
Poor 0%   fair 0%   good 24%   very good 52%   excellent 24%
Basic Statisticts
Poor 0%   fair 4%   good 17%   very good 48%   excellent 31%
Stem Cell Demonstration
Poor 0%   fair 16%   good 50%   very good 17%   excellent 17%
Managing Your Electronic Environment w/BMTbase
poor 8%   fair 0%   good 23%   very good 38%   excellent 31%

Overall Session Comments:
-Disease-specific forms very good.
-Good info-a handout would be good too.
-Core Forms-most thorough, especially for the novice. It wa good to have some vision Wh-4 this is impt..how about the title "Why endure"
-Basics of BMT: could be shorter. Efficient Data Abstracting: needed larger room. Difficult to hear individual sections. Stem Cell Demonstration: could be very short or just an explanation in form of handout-not slides.
-Basics/Registration/Core Forms: very good opportunity to ask all those questions that have been bothering me for some time. Very informative & interesting, need booklet with definitions! Audit Update: Very good information. Stem Cell Demo: misleading if you did not have the program. No training involved and was not apparant at this demonstration.
-Need more clinical information.
-Core Forms: needed more time for Q&A.
-Basics of BMT: very basic. Registration Database: very basic & repetive. Core Forms: lots of info we need! Graft Inserts: we don't need info on labeling, we need info on filling out the forms. Hematopetics covered by Dr Rizzo. Basic Stats: handouts would have really helped! Stem Cell Demo: poorly coordinated.
-Great presentations although seemed a bit rushed. Could have used more time for questions. Basic Stats: great presentation but it should have been earlier in session.
-Efficient Data: somewhat loud-also hated to choose 2 wanted to go to all of them.
-Basic BMT: good presentation, but a little "too basic". Info on cell processing a little technical: no coverage of graft inserts.
-Diane Knutson did an excellent job.
-Graft Inserts: Good overview of stem cell processing, however, no review of graft insert. Disease Specific Forms: would have liked more time alotted for Q&A. Efficient Data: some very good ideas.
-Stem Cell: too technical.
-Graft Inserts: didn't go thru inserts (graft)
-Diane Knutson is very knowledgable and a very good teacher.
-Core Forms: could always use more time. Attended cause of Death-good tools- excellent. The most useful topic/info I received this conference.
-Efficient Data: roundtables were too loud-could not hear at table.
-Stem Cell: not enough time.
-Graft Inserts: nice job. Disease-specific: Very good overview of Multiple Myeloma.

-Could have used more time for Registration & Core. There seemed to be a lot of questions. Graft Inserts: a bit too technical. Disease-Specific: again, a little quick for me.

Meeting Participants
Poor 0%   fair 4%   good 22%   very good 48%   excellent 26%

Attention
Poor 0%   fair 0%   good 20%   very good 47%   excellent 33%

Enthusiasm
Poor 0%   fair 0%   good 27%   very good 43%   excellent 30%

Involvement in Discussion
Poor 0%   fair 0%   good 30%   very good 33%   excellent 37%

Comments & Suggestions for Future Programs:
-I really enjoyed the sessions-maybe break up day one sessions a bit with roundtables, otherwise very good.

-Would like to have been able to attend all 4 roundtables. A bulleted handout & examples for the cause of death discussion was needed. Didn't take advantage of D'Ettas picks but was a very nice touch. This was good information for an out-of-towner.

-Excellent and informative conference. Thank you. Well coordinated.

-Participants: of course we were wonderful! We are doing this stuff...that alone makes us special! Please hold it in the city (ie downtown) even though I won't get to appreciate it!! In general-thanks for the opportunity to "train".

-Could start meetings earlier and finish earlier in day for a little sight seeing. People are more alert in morning and loose concentration in late PM.

-Would have been even better if some from Europe had attended. Need more discussion time. I think the centers should be encouraged to send their teams to these meetings and to be aware of all the changes that occur frequently need to be updated.

-Better or more info about cytogenetics & HLA time typing.

-Great technical details! Break up each day with discussion roundtables.

-These sessions were very interesting for me. I am very appreciative to Diane Knutson for all information and help which she is giving to me.

-Possibly more time on actual forms.

-Except stemsoft software visuals, was too small!

-I particularly liked the sessions presented by Diane Knutson. This was exactly the kind of information and help that I was looking for in this workshop. Thanks for a great job!

-Have a few pictures of BMTx, harvest, etc on the basics talk-maybe some pictures of this lab for lab talk. Why a Sunday??

-Round table discussions could have taken place on the first day of the workshop.

-Thanks for providing this-it was extremely helpful.

-This was really helpful. Thank you very much.

-Have enough time to answer questions along with topic discussions, preferably after speaker is finished with topic. This allows speaker and participants to get good feed back. Round table should not be question and answer-should be a discussion. Operational definitions for data entry needed. Question the ability to retreive reliable DX/TRA information from database (registry). Guidelines for research/reporting resources needed: # hours/form type/pt

-Round table discussions were very helpful in getting tips and ideas from other participants. The whole program was very helpful.

-Would suggest re-organizing Monday afternoon. I think Audit important but unable to attend; attended Stem Soft. Time could be reorganized to get Audit Statistics & Stem Soft perhaps by shortening time slightly for each. Many times Diane referred to data " jusk ask your transplant MD" some data is very specific & there is no variance. If everyone does their own thing, data won't mean anything. It would be beneficial to have a clinical statistician here to answer clinical questions she is unfamiliar with or doesn't know.

-Overall, would have liked more time in those topics dealing directly with the forms. The other topics, while interesting, I can get info on at home. Round table topics very good- but needed more time. Overall, a very worthwhile few days.

-This was very helpful!

-Graft Inserts & Theory was too deep in theory for what I needed to know.

Appendix 4. Publications/Analyses in Progress

4.1 Klein JP, Pelz C, Zhang MJ. Technical Report #28: Modeling random effects for censored data by a multivariate normal regression model. Division of Biostatistics, Medical College of Wisconsin, 1998. (*Biometrics 1999, In press*)

4.2 Park HC, Klein JP. Technical Report #27: Joint modeling of death times and counts using a random effects model. Division of Biostatistics, Medical College of Wisconsin, 1997. *(Paper submitted to Biometrics)*

4.3 Anderson PK, Klein JP, Zhang MJ. Technical Report #23: Testing for center effects in multicenter survival studies: A Monte Carlo comparison of fixed and random effects tests. Division of Biostatistics, Medical College of Wisconsin, 1997. (*Statistics in Medicine 1999, In press*)

4.4 Andersen PK, Horowitz MM, Klein JP, Socie G, Stone JV, Zhang MJ. Technical Report #30: Modeling covariate adjusted mortality relative to a standard population: Does bone marrow transplantation provide a cure? Division of Biostatistics, Medical College of Wisconsin, 1998. (*Statistics in Medicine 1999, In press*)

4.5 Klein JP, Zhang MJ. Technical Report #21: Determining when the survival rates of two treatments are the same based on a censored data regression model. Division of Biostatistics, Medical College of Wisconsin, 1996. (*J Planning and Inference, 1999, In press*)

4.6 Klein JP, Zhang MJ. Technical Report #29: Confidence bands for the difference of two survival curves under proportional hazards model. Division of Biostatistics, Medical College of Wisconsin, 1998. *(Submitted)*

4.7 Klein JP, Qian C. Technical Report #15: Modeling multistate survival illustrated in bone marrow transplantation. Division of Biostatistics, Medical College of Wisconsin, 1996. *(1996 Proc ASA Conf 93-102, 1996.*

4.8 Zhang MJ. Technical Report #24: Grouped failure times, tied failure times: Two contributions to the Encyclopedia of Biostatistics. Division of Biostatistics, Medical College of Wisconsin, 1997.

4.9 Klein JP. Survival distributions and their characteristics: A contribution to the Encyclopedia of Biostatistics. Division of Biostatistics, Medical College of Wisconsin, 1997.

4.10 Johnson RA, Klein JP. Technical Report #26: Regression models for survival data. Department of Statistics, University of Wisconsin-Madison and Division of Biostatistics, Medical College of Wisconsin, 1997.

Appendix 4, continued.

4.11 Antman KH, Rowlings PA, Vaughan WP, Pelz CJ, Fay JW, Fields KK, Freytes CO, Gale RP, Hillner BE, Holland HK, Kennedy MJ, Klein JP, Lazarus HM, McCarthy PL Jr, Saez R, Spitzer G, Stadtmauer EA, Williams SF, Wolff S, Sobocinski KA, Armitage JO, Horowitz MM. High-dose chemotherapy with autologous hematopoietic stem cell support for breast cancer in North America. *J Clin Oncol* 15:1870-1879, 1997.

4.12 Rowlings PA, Williams SF, Antman KH, Fields KK, Fay JW, Reed E, Pelz CJ, Klein JP, Sobocinski KA, Kennedy MJ, Freytes CO, McCarthy PL Jr., Herzig RH, Stadtmauer EA, Lazarus HM, Pecora AL, Bitran JD, Wolff SN, Gale RP, Armitage JO, Vaughan WP, Spitzer G, Horowitz MM. Factors correlated with progression-free survival after high-dose therapy and hematopoietic stem cell transplantation for metastatic breast cancer. *JAMA*, 1999. In press.

4.13 Berry DA, Broadwater G, Perry MC, Aisner J, Costanza M, Parnes H, Henderson IC, Norton L, Antman K, Klein JP, Horowitz MM. Conventional vs. high-dose therapy for metastatic breast cancer: comparison of Cancer and Leukemia Group B (CALGB) and Blood and Marrow Transplant Registry (ABMTR) patients. Abstract submitted for 1999 Annual Meeting of the American Society of Clinical Oncology.

4.14 ABMTR study #BC98-03. Preliminary results: Autotransplants for stage 2/3 breast cancer.

4.15 McCarthy PL, Jr., Hurd DD, Rowlings PA, Murphy SC, Antman KH, Armitage JO, Cirenza E, Crump M, Doroshower J, Freytes CO, Gale RP, Kalman LA, Lazarus HM, Vaughan WP, Weinberger B, Wiemann MC, Horowitz MM. Autotransplants in thirteen men with breast cancer (submitted).

4.16 Bennett CL, Waters TM, Stinson TJ, Almagor O, Sobocinski KA, Klein JP, Rowlings PA, Horowitz MM. Analysis of short-term costs of allogeneic transplantation: results from the International Bone Marrow Transplant Registry/Northwestern University economic data base project. Blood 92 (Suppl 1): 137a, 1998.

4.17 Chen CS, Seidel K, Armitage JO, Fay JW, Appelbaum FR, Horowitz MM, Shpall EJ, Weiden PL, Antman KS, Champlin RE, Kersey JH, Sullivan KM. Safeguarding the administration of high-dose chemotherapy: A national practice survey by the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 3 (6):331-340, 1997.

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BY

DIVISION OF BIOSTATISTICS

DIVISION OF BIOSTATISTICS

MEDICAL COLLEGE OF WISCONSIN

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MODELING RANDOM EFFECTS FOR CENSORED DATA BY A MULTIVARIATE NORMAL REGRESSION MODEL

BY

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BY

DIVISION OF BIOSTATISTICS
THE MEDICAL COLLEGE OF WISCONSIN

TECHNICAL REPORT 28

Abstract

A normal regression model with a frailty factor to account for statistical dependence between the observed survival times is introduced. This model, as opposed to other frailty models, has survival times which, conditional on the frailty, have an accelerated failure time representation. The dependence properties of this model are discussed and maximum likelihood estimation of model's parameters is considered. A number of examples are considered to illustrate the approach.

1. Introduction

In the analysis of survival data a common assumption that is made is that the life histories for individuals under study are all statistically independent (at least conditionally on the observed fixed time covariates). In some cases, when individuals within some subgroup share common unmeasured traits, this assumption may not be valid. For example, the survival times of siblings or married couples in human studies or litter mates in animal studies may be associated.

Recently, a number of authors have proposed using the so called shared frailty model to account for the dependence between the event times. In this model all individuals within a group share a common unobservable random effect, the frailty, which acts multiplicatively on each individual's hazard rate. That is, for the ith individual, with covariates Z_i, in a group of size M, we model the hazard rate of the event time, X_i, by

$$h(t \mid Z_i, W) = W \, h(t \mid Z_i) \, , i = 1,...,M.$$

The individual hazard rates, given the frailty, are modeled by assuming a proportional hazards regression model with either a known (typically Weibull or piecewise constant) baseline hazard rate or by an arbitrary baseline hazard rate which yields an extension to the Cox (1972) regression model (See Klein and Moeschberger 1997 for examples). Conditional on the unobserved frailty, individuals within a group are assumed to be independent.

Common models for the frailty are the gamma distribution (c.f. Clayton (1991), Klein (1992) or Nielsen et al (1992)), the positive stable distribution (See Hougaard(1986a), Wang et al (1995)), the inverse Gaussian (c.f. Hougaard (1986b), Klein et al (1992)), and the log normal distribution (McGilchrist and Aisbett (1991) or Yau and McGilchrist (1997)).

In this note we take an alternative approach to modeling dependence between the survival times of group members. We model survival within a group, given an unobserved frailty, by an accelerated failure time model, or more equivalently we model the logarithm of the event time as a linear function of the covariates. That is, for the jth individual in a group, we model $Y_j = \log(X_j)$, by

$$Y_j = \mu + \beta^t Z_j + E_j, \; j=1,...,M.$$

Here E_j are mean 0 random variables. Under the usual accelerated failure model the E_j's are assumed to be an independent and identically distributed sample from some distribution such as the extreme value distribution (Weibull Regression model), the logistic (Log logistic Regression) or the normal distribution (log normal regression). Estimation for these models is available in most

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packages such as SAS and BMDP. To model association within a group we shall assume that the E_j's can be decomposed into a sum of an individual specific error, W_i and a group specific error, W_0. That is,

$$E_j = \omega^{1/2} W_j + \theta^{1/2} W_0.$$

Assuming the variance of W_j and W_0 are equal to 1, then ω is the within subject variance and θ the between subject variation. In this model W_i can be thought of as the measurement error specific to the ith individual and W_0 as the unmeasured uncertainty common to all individuals within a group. The correlation between the lifetimes within a group is $\theta/(\theta+\omega)$ and the model reduces to the usual accelerated failure time model when $\theta=0$.

In the sequel we consider this model when the W's follow a standard normal distribution. This leads to a, conditional on W_0, log normal regression model for the survival times X_i. Unconditionally, the joint distribution of the X_i's has a multivariate log normal distribution. The log normal distribution has a hazard rate which is initially increasing and then decreasing. The Log normal has been suggested as a model for the survival times of several chronic diseases such as Hodgkin's disease (Osgood 1958), chronic leukemia (Feinleib and MacMahon 1960), and onset times of Alzheimer's disease (Horner 1987). The multivariate log normal model after a quadratic transformation (with no censoring) was used by Herskind et al (1996) to model the longevity of Danish twins. The " hump-shaped" hazard rate is often used in modeling survival after successful surgery where there is an initial increase in risk due to infection, hemorrhaging, or other complications just after the procedure, followed by a steady decline in risk as the patient recovers. We have found the log normal distribution gives a good fit when modeling the bone marrow transplant recovery process where patients are at high risk initially after transplant when their immune systems are depleted but have a decreased risk once the new cells engraft. The model is not appropriate, however, when the conditional hazard rates are monotone as is commonly the case in modeling the onset times of solid organ cancers.

In the next section we investigate the dependence properties of this model. In Section 3 we derive maximum likelihood estimators for the parameters of the model when the data is right censored. In Section 4 we show several examples of the use of this model and in Section 5 we present a crude graphical method checking the modeling assumptions.

2. The Multivariate Normal Regression Model

For each of the M individuals in a group we assume that the logarithm of their survival times $Y_j = \ln[X_j]$ is

$$Y_j = \mu + \beta^t Z_j + \theta^{1/2} W_j + \omega^{1/2} W_0, \ j=1,...,M. \tag{2.1}$$

Suppose that $W_0, W_1, ..., W_M$ are an independent and identically distributed sample from a standard normal distribution. Then the joint distribution of $(Y_1, ..., Y_M)$ is M-variate normal with $E[Y_i] = \mu + \beta^t Z_j$, $Var[Y_j] = \omega + \theta$ and $Cov[Y_j, Y_k] = \theta$, $j \neq k$. For this model the correlation between the log survival times of any two members of the group is $\rho = \theta/(\theta+\omega)$ and Kendall's τ is $2Sin^{-1}(\rho)/\pi$. Note that the correlation and Kendall's τ are both zero when θ is equal to 0 and tend to 1 as θ tends to infinity.

On the original time scale $(X_1, ..., X_M)$ has a M-variate log normal distribution (See Jones and Miller 1966). We have

$$E[X_j] = \exp\{\mu + \beta^t Z_j + (\omega+\theta)/2\}, \ j=1,...,M;$$

$$Var[X_j] = \exp\{2(\mu + \beta^t Z_j) + \omega + \theta\}[\exp\{\omega + \theta\} -1], \ j=1,...,M;$$

$$Cov[X_j, X_k] = [\exp\{\theta\} - 1] \exp\{(\mu + \beta^t Z_j) + (\mu + \beta^t Z_k) + \omega + \theta\}, \ j \neq k;$$

and

$$Corr[X_j, X_k] = \frac{[\exp\{\theta\} - 1]}{[\exp\{\omega + \theta\} -1]}, \ j \neq k.$$

Note that the correlation between X_j and X_k is a monotone increasing function of θ with a correlation of zero when θ equals zero and a limit of $\exp\{-\omega\}$ as θ tends to infinity. Since the marginal distributions of the X's have a log normal distribution, the correlation coefficient may not be the best parameter to measure association. However, Kendall's tau is unaffected by a common monotone transformation applied to the each margin so that the value of τ is the same as for the log survival times. Note that τ is also monotone in θ, but the upper limit of the range of τ is 1 which corresponds to the maximal association one can have.

3. ESTIMATION OF MODEL PARAMETERS

Suppose we have data on G subgroups each following the model (2.1). Let M_i be the number of subjects in the ith group. While it is permissible for M_i to be one we require that at least one subgroup have more than one member, otherwise θ and ω are not identifiable from the data. For the jth subject in the ith group let T_{ij} be their on study time; δ_{ij} be the indicator of whether they died ($\delta_{ij} = 1$) or were censored ($\delta_{ij} = 0$); and let Z_{ij} be their (p+1) - vector of covariate values,

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$j=1,...,M_i$, $i=1,...,G$. For convenience we take the first element of $\mathbf{Z}_{ij}$ to be 1 to account for the intercept term in the model.

To construct the contribution to the likelihood for the ith group let $d_i = \sum_{j=1}^{M_i} \delta_{ij}$ be the number of deaths in the ith group. If all members of the group die ($d_i = M_i$) then the contribution to the likelihood is the joint density function of $\mathbf{Y}_i = (Y_{i1}, ...,Y_{iM_i})^t$ evaluated at $\ln[T_{ij}]$, $j=1,...,M_i$. If there is any censored observation between the M_i individuals then rewrite $\mathbf{Y}_i = (\mathbf{Y}_i^C, \mathbf{Y}_i^D)^t$, where $\mathbf{Y}_i^D$ is the d_i vector of death times and $\mathbf{Y}_i^C$ is the (M_i-d_i) vector of censored observations. Using standard results on the multivariate normal distribution given in Andersen (1958) it is easy to show that the conditional distribution of $\mathbf{Y}_i^C$ given $\mathbf{Y}_i^D$ is (M_i-d_i) -variate normal with

$$E[Y_{ik}^C|\mathbf{Y}_i^D] = \beta^t \mathbf{Z}_{ik} + \frac{\theta}{d_i\theta+\omega} \sum_{j=M_i-d_i+1}^{M_i} [Y_{ij} - \beta^t \mathbf{Z}_{ij}], \text{ for } k=1,...,(M_i-d_i); \tag{3.1}$$

$$Var[Y_{ik}^C|\mathbf{Y}_i^D] = \omega + \frac{\theta\,\omega}{d_i\theta+\omega}, \text{ for } k=1,...,(M_i-d_i); \tag{3.2}$$

and

$$Cov[Y_{ik}^C, Y_{ik'}^C|\mathbf{Y}_i^D] = \frac{\theta\,\omega}{d_i\theta+\omega}, \text{ for } k',k=1,...,(M_i-d_i),\ k'\neq k. \tag{3.3}$$

The contribution to the likelihood for the ith group is the product of the density function for $\mathbf{Y}_i^D$ times the conditional survival function of $\mathbf{Y}_i^C$ given $\mathbf{Y}_i^D$ evaluated at $Y_{ij}=\ln[T_{ij}]$. The conditional survival function of $\mathbf{Y}_i^C$ given $\mathbf{Y}_i^D$ involves evaluation of a (M_i-d_i) dimensional integral. To reduce the dimesionality of this integral, which must be evaluated numerically, we use the following lemma which is motivated by results in Chapter 35, Section 4 of Johnson and Kotz (1972), to reduce the dimensionality of the integal to be evaluated.

Lemma Let $\mathbf{X}$ have a k-variate normal distribution with mean 0 and correlations equal to $\rho \geq 0$. Then

$$P[X_1 \geq x_1,...,X_k \geq x_k] = \int_{-\infty}^{\infty} \phi(u) \prod_{j=1}^{k} \left\{ 1-\Phi[\frac{x_j-u\,\rho^{1/2}}{(1-\rho)^{1/2}}] \right\} du, \tag{3.4}$$

where $\phi(u) = \dfrac{1}{(2\pi)^{1/2}} \exp\{-u^2/2\}$ and $\Phi(u) = \displaystyle\int_{-\infty}^{u} \phi(v)dv$ are the standard normal density and distribution functions.

Proof:

Let $U_0, U_1, ... U_k$ be independent standard normal random variables then

$$X_j = \rho^{1/2} U_0 + (1-\rho)^{1/2} U_j \, , \, j=1,...,k.$$

The inequality $\{X_j \geq x_j\}$ is equivalent to $U_j \geq \dfrac{X_j - \rho^{1/2} U_0}{(1-\rho)^{1/2}}$ which leads to the representation (3.4).

■

Applying the above lemma and 3.1-3.3 gives a contribution to the log likelihood for the ith group, i=1,...,G, of $L_i = L_i^D + L_i^C$, where L_i^D is the contribution of the d_i deaths given by

$$L_i^D = -\frac{d_i}{2} \ln[2\pi] - \left(\frac{1}{2}\right)\{ (d_i-1)\ln[\omega] + \ln[d_i\,\theta + \omega]\} - \frac{S_{2i}(\beta)}{2\omega} + \frac{\theta\, S_{1i}(\beta)^2}{2\omega\,(d_i\,\theta + \omega)}$$

$$(3.5)$$

with $S_{1i}(\beta) = \displaystyle\sum_{j=1}^{M_i} \delta_{ij}\, \{\ln[T_{ij}] - \beta^t Z_{ij}\}$ and $S_{2i}(\beta) = \displaystyle\sum_{j=1}^{M_i} \delta_{ij}\, \{\ln[T_{ij}] - \beta^t Z_{ij}\}^2;$ and

$$L_i^C = \ln \int_{-\infty}^{\infty} \phi(u) \prod_{k=1}^{M_i - d_i} \left\{ 1 - \Phi\left[\frac{\ln[T_{ik}] - \beta^t Z_{ik} - \dfrac{\theta}{d_i\theta + \omega} S_{1i}(\beta)}{\omega^{1/2}} - \frac{\theta^{1/2}}{(d_i\theta + \omega)^{1/2}} u\right] \right\} du.$$

$$(3.6)$$

The overall log likelihood is the sum of the log likelihoods for the individual groups. In the Appendix we give the first and second partial derivatives of the likelihood with respect to the parameters.

To maximize the log likelihood we use the following procedure. First, we find the maximum likelihood estimates and the value of the log likelihood under an assumption of independence using a Newton-Raphson algorithm. This is equivalent to maximizing the likelihood under the constraint that θ is equal to zero. The derivatives in the appendix can be used to

implement this step of the algorithm or a statistical package such as SAS or BMDP can be used to find these estimates. In using our representation (3.6) or one of the derivatives of this integral there is still a univariate integral to evaluate. In our examples we used a 20 point Gauss-Hermite formula (See Abramowitz and Stegun, 1970) for this integration. We found in all our examples that the approximations we use give us excellent agreement with the estimates and likelihoods when $\theta=0$ obtained from both SAS and BMDP.

The second step of the procedure is a crude examination of the profile log likelihood as a function of θ. This is done to find starting values for the implementation of a full Newton-Raphson maximization routine. The likelihood is maximized with respect to ω and β for a fixed value of θ. The profile likelihood is computed for a number of values of θ. The value of θ which gives the maximum in this search is used in the third step of the procedure which is a full implementation of the Newton-Raphson algorithm. Using the estimates of ω and β found when $\theta = 0$ as starting points in a Newton-Raphson algorithm is not possible since the likelihood has a stationary point at 0. Once the estimates of (θ, ω, β) are found the negative of the final Hessian matrix is inverted to find the observed information matrix which yields standard errors of the maximum likelihood estimators.

4. Examples

To illustrate this technique we shall consider three examples. The first example is based on a tumorigenesis study of fifty litters of male rats reported in Mantel el al. (1977). For each litter one rat was selected to receive the drug and the other two rats were placebo treated controls. One might expect that the times to tumor formation for rats in a given litter would be correlated due to shared genetic or environmental effects. Time to tumor was measured in weeks and death before tumor occurrence yields a right-censored onservation. There is a single covariate in the model reflecting the drug effect. The results are in Table 1 for the Multivariate Normal Regression Model and for the model assuming independence between litter mates.

Table 1

Results of Fitting Multivariate Normal Model to the Litter-Matched Rats

Effect	Multivariate Normal Model		Independence Model	
	Estimate	Standard Error	Estimate	Standard Error
Intercept	4.9654	0.0960	4.9692	0.0926
Drug	-0.2365	0.0972	-0.2464	0.1083
Within Subject Variance(ω)	0.1658	0.0486	0.2333	0.0583
Frailty (θ)	0.0691	0.0435		
Ln Likelihood	-70.1020		-72.0130	

The likelihood ratio test of hypothesis of no association between litter mates ($\theta=0$) has a chi-square of 3.82 with one degree of freedom. The p-value is 0.05 which suggests that there is some evidence of a litter effect. To measure the strength of the association between litter mates one can use any one of three measures. The first is the correlation between the log survival times estimated by

$$\hat{\rho}_1 = \frac{\hat{\theta}}{(\hat{\theta}+\hat{\omega})}, \tag{4.1}$$

which has an estimated variance of

$$\hat{V}[\hat{\rho}_1] = \frac{\hat{\omega}^2 V[\hat{\theta}] + \hat{\theta}^2 V[\hat{\omega}] + 2\hat{\omega}\hat{\theta} Cov[\hat{\theta},\hat{\omega}]}{(\hat{\theta}+\hat{\omega})^4}. \tag{4.2}$$

The second is the correlation between the survival times which is estimated by

$$\hat{\rho}_2 = \frac{\exp[\hat{\theta}] - 1}{\exp[\hat{\theta}+\hat{\omega}] - 1}, \tag{4.3}$$

which has an estimated variance of

$$\hat{V}[\hat{\rho}_2] = \frac{\exp[\hat{\theta}]}{(\exp[\hat{\theta}+\hat{\omega}] - 1)^4} \tag{4.4}$$

$$\times \{\exp[2\hat{\omega}](1-\exp[\hat{\theta}])^2 V[\hat{\theta}] + (\exp[\hat{\omega}]-1)^2 V[\hat{\omega}] + 2\exp[\hat{\omega}](1-\exp[\hat{\theta}])(\exp[\hat{\omega}]-1) Cov[\hat{\theta},\hat{\omega}]\}$$

The final measure of association is Kendall's τ which is estimated by

$$\hat{\tau} = \frac{2 \operatorname{Sin}^{-1}[\hat{\rho}_1]}{\pi} \tag{4.5}$$

which has an estimated variance of

$$\hat{V}[\hat{\tau}] = \frac{4 \ \hat{V}[\hat{\rho}_1]}{\pi(1 - \hat{\rho}_1^2)} \tag{4.6}$$

Estimates of the asymptotic variance of $\hat{\theta}$ and $\hat{\omega}$ are available from the observed information matrix. In this example we have the following estimates of the strength of association.

Parameter	Estimate	Standard Error	95% Confidence Interval
ρ_1	0.2942	0.0443	(0.2074,0.3810)
ρ_2	0.2702	0.0472	(0.1778,0.3627)
τ	0.1901	0.0361	(0.1193,0.2609)

This data was previously analyzed by Andersen et al (1996) using a multiplicative frailty model. For this model, conditional on a gamma distributed frailty, W, the life times of litter mates were assumed to be independent with a hazard rate $W\lambda_0(t)\exp[\beta Z_j]$, $j=1,..,M$. $\lambda_0(t)$ was either treated non-parametrically or was modeled using a Weibull or piecewise constant hazard rate. Using this model the likelihood ratio statistics for testing the hypothesis of independence were found to be 1.52 for the semi-parametric model; 1.62 for a Weibull model; and 1.58 and 1.52 for piecewise constant models with 6 or 31 intervals, respectively. All models give an estimate of Kendall's tau of about 0.19 in close agreement with the estimates obtained from the multivariate normal model. The standard error of these estimates, however, was about 0.15 which is considerably larger than that obtained from the log normal model.

The log normal distribution is not typically used for cancer incidence data since its hazard rate is decreasing after some point in time. In this example, however, the hazard rate has yet to start to decline at 4 years which is well past the expected lifetime of rats used in the study. This may explain why this model appears to fit the data reasonably well.

A second example is based on data found in Batchelor and Hackett (1970) who report the results of a study of 16 acutely burned patients treated with skin allografts. Patients received from one to four grafts. There were a total of 34 grafts among the 16 patients of which 30 failed. For each graft the time in days to rejection of the graft was recorded as well as an indicator variable Z which had a value of 1 if the graft was a good match of HLA skin type and 0 if it was a poor match. Thirty of the thirty-four grafts were rejected. The survival times of some grafts were censored by the death of the patient. It is reasonable to assume that grafts on a given patient may

have rejection times which are correlated. The results of fitting the multivariate normal and independence model to this data are found in Table 2.

Table 2
Results of Fitting Multivariate Normal Model to the Skin-Graft Data

Effect	Multivariate Normal Model		Independence Model	
	Estimate	Standard Error	Estimate	Standard Error
Intercept	3.050	0.129	3.060	0.121
HLA Match	0.501	0.140	0.556	0.183
Within Subject Variance(ω)	0.129	0.046	0.271	0.0732
Frailty (θ)	0.140	0.077	-	
Ln Likelihood	-24.05		-27.10	

The likelihood ratio test of hypothesis of no association between the survival of grafts on the same person has a chi-square of 6.1 which has a p-value of 0.014, which suggests that there is somewhat strong evidence of a correlation between the graft rejection times on a given patient. The strength of this association, as measured by ρ_1, ρ_2 and τ is as follows:

Parameter	Estimate	Standard Error	95% Confidence Interval
ρ_1	0.521	0.058	(0.407, 0.635)
ρ_2	0.487	0.140	(0.357, 0.618)
τ	0.349	0.197	(0.251, 0.447)

Here we see 95% confidence intervals for all three measures are bounded away from zero and that for all three parameters the point estimate suggests a strong association of rejection times within a given patient.

This model was also fit by Andersen et al (1996) using a semi parametric multiplicative gamma frailty model. They found that the likelihood ratio chi square for testing the hypothesis of no association was 1.34 which, as opposed to the multivariate normal model, is not significant. Their estimate of τ was 0.217 with a standard error of 0.178 (95% confidence interval: (-0.13,0.566). A gamma frailty Weibull model found a likelihood ratio chi square for the test of no association of 11.4 which is highly signficant. The estimate of τ for the Webull model is 0.49 with a 95% confidence interval of (0.257,0.727) which is in agreement with the log normal model. In this case the sample size is quite small and the number of distinct event times (7) is very small

which suggests that a semi parametric model may not have sufficient power to detect the association between skin graft survival on the same person.

For the third example we consider a set of 1571 selected from the Framingham Heart Study (See Dawber 1980 for details). Subjects were included in the sample if they reach age 45 with no prior evidence of coronary heart disease. Patients were followed to first evidence of coronary heart disease (250 cases) or until their 10th cycle of Framingham exams. Covariates, measured at the exam closest to age 45, included in the model are body mass index (BMI) measured in kg/m^2, cholesterol level (CHOL) measured in mg/dL, sex (male -1, female-0), smoking status (smoker-1) and hypertension status (HYP) (normal -0, hypertensive or borderline hypertensive-1). The time variable used was the patients onstudy time measured from age 45 and event of interest is the occurrence of coronary heart disease.

In this example, siblings who share a common genetic code and a common environment in childhood may have event times which are correlated. In the study there were 1401 sib groups with 1-4 members per group. The results of the fit of the log normal distribution are as follows:

Table 3
Results of Fitting Multivariate Normal Model to the Framingham Heart Study Data

Effect	Multivariate Normal Model		Independence Model	
	Estimate	Standard Error	Estimate	Standard Error
Intercept	4.6168	0.0766	4.6149	0.0765
BMI	-0.0434	0.0238	-0.0435	0.0238
CHOL	-0.0493	0.0195	-0.0484	0.0194
SMOKE	-0.0451	0.0190	-0.0707	0.0181
SEX	-0.0404	0.0181	-0.0872	0.0173
HYP	-0.0443	0.0172	-0.0451	0.0190
Within Subject Variance(ω)	0.0405	0.0070	0.0437	0.0044
Frailty (θ)	0.0032	0.0058		
Ln Likelihood	-338.14		-338.29	

In this example the likelihood ratio chi-square test of the hypothesis is 0.31. In this example, as in the other examples, the interpretation of the risk coefficients in the independence and dependence model are different. In the independence model the effect of a risk factor is compared between subjects in the study with different values of the covariate, while in the multivariate normal model the comparison is within a given group. For the above example we see that the effect of smoking is larger in the independence model than in the multivariate normal

model. Since smoking behavior tends to be similar between siblings, perhaps determined in childhood, this is not too surprising. In the independence model, part of the magnitude of the β is reflecting the family effect, while in the multivariate normal model the comparison between smokers and non smokers is on siblings. Similarly, the effect of sex is larger in the independence model which might be expected since in most sibships of size two or larger the members were of the same sex. For the other factors there is relatively little difference between the effects of the covariates under the two models. The total variance in the independence model of 0.0437 which is approximately equal to the within sibship variance of 0.0032 and the between group variance of 0.0405, so that the multivariate normal model allows one to examine in more detail the various contributions to the variance.

5. Checking For Model Fit

The problem of checking for the fit of the multivariate normal model is difficult. A crude method of checking the fit of the model is to use the fact that marginally each log survival time follows a normal distribution with mean $\beta^t Z_j$ and variance $\omega + \theta$. To check the model we randomly select one observation from each group and define the generalized residual (See Klein and Moeschberger (1997)) by

$$R_k = \frac{Y_k - \beta^t Z_k}{[\omega + \theta]^{1/2}}, \tag{4.1}$$

where Y_k is the randomly selected log survival time from the kth group, k=1,...,G. The Y_k's are independent since only one observation comes from each group. If the multivariate normal model holds then the sample (R_k, δ_k) should be a censored sample from a standard normal distribution. This can be checked by a normal hazard plot. That is, we plot $\Phi^{-1}[1-\exp[-\hat{\Lambda}(R_k)]]$ versus log R_k, where $\hat{\Lambda}()$ is the Nelson-Aalen estimator of the cumulative hazard rate of the generalized residuals. If the normal model holds marginally then each hazard plot should be close to the 45° line.

Figure 1 shows the hazard plots for 10 samples from the fitted model for the Framingham Heart Study example. Here we see that the hazard plots are all clustered close to the 45° line and there is no evidence of a lack of fit of the model.

Figures 2 and 3 show the plots of ten samples of residuals from the litter matched tumorigenesis study and the skin graft study respectively. Here the sample sizes for each residual curve are small (size 50 and 16, respectively) so there is a high degree of uncertainty in these graphs. For the tumorigenesis study it appears that the multivariate normal provides a reasonable fit to the data. The log normal distribution is not typically used for cancer incidence data since its hazard rate is decreasing after some point in time. In this example, however, the hazard rate has yet to start to decline at 4 years which is well past the expected lifetime of rats used in the study.

This may explain why this model appears to fit the data reasonably well. For the skin graft data most of the replicates lie above the 45° line, particularly around a log residual value of zero suggesting that the multivariate normal model is suspect.

One may try to make a normal hazard plot using all the residuals or make separate log normal hazard plots at each level of the covariates. Such plots are difficult to interpret when there is a significant association between individuals within groups since the residuals no longer are an independent sample from the log normal distribution.

6. Discussion

In this note we have presented an alternative to the multiplicative frailty model which allows an investigator to access the strength of association between event times and to adjust regression coefficients for possible random effects. Here the effect of the common group effect is additive on the log failure times within a group. On the original time scale the effect of the shared random effect is to change the time scale for all members of the group by a factor $\exp\{\theta^{1/2}W_0\}$. This should be contrasted to the usual random effects model where the frailty acts multiplicatively on the hazard rate of each group member.

In this paper we have based estimation on a log normal model for the frailties. This model was used, primarily, since the joint distribution of the log event times within a group is well known. Other distributions, such as the standard extreme value distribution or the logistic distribution could be used as models for the W's. These would lead to multivariate generalizations of the Weibull and log logistic distributions on the original time scale. Of course the Weibull generalization of the accelerated failure model will yield a model equivalent to a multiplicative frailty model.

This model is of use when there are some groups that have at least two members. When the frailty is used to describe heterogeneity due to omitting covariates in a univariate regression model (See Keiding et al. 1997) this approach is not feasible since it is impossible to separate the random effect, W_0, from the error distribution, W_1, when there is a single observation in each group.

The multivariate log normal model can be extended in a natural way to allow for two independent random effects acting on each individual. For example, one may wish to model simultaneously the association of death times between siblings who share a common genetic code and between married couples who share a common environmental effect.

Acknowledgments

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Appendix

The partial derivatives of L_i^D with respect to the parameters are

$$\frac{\partial L_i^D}{\partial \theta} = -\frac{d_i}{2[d_i\theta + \omega]} + \frac{S_{1i}(\beta)^2}{2[d_i\theta + \omega]^2} \qquad (A.1)$$

$$\frac{\partial L_i^D}{\partial \omega} = -\frac{d_i-1}{2\omega} - \frac{\omega}{2[d_i\theta + \omega]} + \frac{S_{2i}(\beta)}{2\omega^2} - \frac{\theta\, S_{1i}(\beta)^2\, (d_i\theta + 2\omega)}{2\,\omega^2\,[d_i\theta + \omega]^2} \qquad (A.2)$$

$$\frac{\partial L_i^D}{\partial \beta_k} = \frac{S_i^{(k)}(\beta)}{\omega} - \frac{\theta S_{1i}(\beta)\,[\sum\limits_{j=1}^{M_i}\delta_{ij}Z_{ijk}]}{\omega\,[d_i\theta + \omega]}, \qquad k=0,\dots,p \qquad (A.3)$$

$$\frac{\partial^2 L_i^D}{\partial \theta^2} = \frac{d_i^2}{2[d_i\theta + \omega]^2} - S_{1i}(\beta)^2\,\frac{d_i}{[d_i\theta + \omega]^3} \qquad (A.4)$$

$$\frac{\partial^2 L_i^D}{\partial \theta \partial \omega} = \frac{d_i}{2[d_i\theta + \omega]^2} - \frac{S_{1i}(\beta)^2}{[d_i\theta + \omega]^3} \qquad (A.5)$$

$$\frac{\partial^2 L_i^D}{\partial \theta \partial \beta_k} = -\frac{S_{1i}(\beta)\,[\sum\limits_{j=1}^{M_i}\delta_{ij}Z_{ijk}]}{[d_i\theta + \omega]^2}, \quad k=0,\dots,p \qquad (A.6)$$

$$\frac{\partial^2 L_i^D}{\partial \omega^2} = \frac{d_i-1}{2\omega^2} + \frac{1}{2[d_i\theta + \omega]^2} - \frac{S_{2i}(\beta)}{\omega^3} + \frac{\theta\, S_{1i}(\beta)^2\,[(d_i\theta)^2 + 3\,d_i\theta\omega + 3\omega^2]}{\omega^3\,[d_i\theta + \omega]^3} \qquad (A.7)$$

$$\frac{\partial^2 L_i^D}{\partial \omega \partial \beta_k} = -\frac{S_i^{(k)}(\beta)}{\omega^2} + \frac{S_{1i}(\beta)\,[\sum\limits_{j=1}^{M_i}\delta_{ij}Z_{ijk}]\,\theta\,(d_i\theta + 2\omega)}{\omega^2\,[d_i\theta + \omega]^2}, \quad k=0,\dots,p \qquad (A.8)$$

$$\frac{\partial^2 L_i^D}{\partial \beta_k \partial \beta_{k'}} = -\frac{\sum\limits_{j=1}^{M_i}\delta_{ij}\, Z_{ijk'}Z_{ijk}}{\omega} + \frac{\theta\,[\sum\limits_{j=1}^{M_i}\delta_{ij}Z_{ijk'}][\sum\limits_{j=1}^{M_i}\delta_{ij}Z_{ijk}]}{\omega\,[d_i\theta + \omega]}, \qquad k,\,k'=0,\dots,p \quad (A.9)$$

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Where $S_i^{(k)} = \sum\limits_{j=1}^{M_i} \delta_{ij} \{\ln[T_{ij}] - \beta^t Z_{ij}\} Z_{ijk}$.

To express the partial derivatives of L_i^C let

$$i_i(\theta, \omega, \beta) = \int\limits_{-\infty}^{\infty} \phi(u) P(u: \theta, \omega, \beta) du,$$

$$P(u: \theta, \omega, \beta) = \prod\limits_{k=1}^{M_i - d_i} \left\{ 1 - \Phi\left[\frac{\ln[T_{ik}] - \beta^t Z_{ik}}{\omega^{1/2}} - \frac{S_{1i}(\beta)\theta}{\omega^{1/2}[d_i \theta + \omega]} - \frac{\theta^{1/2}}{[d_i \theta + \omega]^{1/2}} u\right] \right\},$$

$$h_{ij}[u:\theta, \omega, \beta] = \frac{-d\log[1 - \Phi(x)]}{dx} \quad \text{and} \quad h_{ij}'[u:\theta, \omega, \beta] = \frac{d^2\log[1 - \Phi(x)]}{dx^2}$$

evaluated at $x = \dfrac{\ln[T_{ij}] - \beta^t Z_{ij}}{\omega^{1/2}} - \dfrac{S_{1i}(\beta)\theta}{\omega^{1/2}(d_i\theta + \omega)} - \dfrac{\theta^{1/2}}{(d_i\theta + \omega)^{1/2}} u.$

The partial derivatives of $i_i(\theta, \omega, \beta)$ with respect to the parameters are

$$\frac{\partial i_i(\theta, \omega, \beta)}{\partial \theta} = \sum\limits_{j=1}^{M_i - d_i} \int\limits_{-\infty}^{\infty} \phi(u)\left[\frac{\omega^{1/2}S_{1i}(\beta)}{(d_i\theta + \omega)^2} + u\frac{\omega}{2\theta^{1/2}(d_i\theta + \omega)^{3/2}}\right] h_{ij}[u: \theta, \omega, \beta] P(u: \theta, \omega, \beta) du; \quad (A.12)$$

$$\frac{\partial i_i(\theta, \omega, \beta)}{\partial \omega} = \sum\limits_{j=1}^{M_i - d_i} \int\limits_{-\infty}^{\infty} \phi(u)\left[\frac{\ln[T_{ij}] - \beta^t Z_{ij}}{2\omega^{3/2}} - \frac{S_{1i}(\beta)(3\omega\theta + d_i\theta^2)}{2\omega^{3/2}(d_i\theta + \omega)^2} - u\frac{\theta^{1/2}}{2(d_i\theta + \omega)^{3/2}}\right]$$

$$\times h_{ij}[u: \theta, \omega, \beta] P(u: \theta, \omega, \beta) du; \quad (A.13)$$

$$\frac{\partial i_i(\theta, \omega, \beta)}{\partial \beta_k} = \sum\limits_{j=1}^{M_i - d_i} \int\limits_{-\infty}^{\infty} \phi(u)\left[\frac{Z_{iik}}{\omega^{1/2}} - \frac{\theta \left[\sum\limits_{j=1}^{M_i} \delta_{ij} Z_{ijk}\right]}{\omega^{1/2}(d_i\theta + \omega)}\right] h_{ij}[u, \theta, \omega, \beta] P(u: \theta, \omega, \beta) du; \quad k=0,...,p$$

$$(A.14)$$

$$\frac{\partial^2 i_i(\theta, \omega, \beta)}{\partial \theta^2} = -\sum\limits_{j=1}^{M_i - d_i} \int\limits_{-\infty}^{\infty} \phi(u)\left[\frac{2d_i\omega^{1/2}S_{1i}(\beta)}{(d_i\theta + \omega)^3} + u\frac{4d_i\theta\omega + \omega^2}{4\theta^{3/2}(d_i\theta + \omega)^{5/2}}\right] h_{ij}[u:\theta, \omega, \beta] P(u: \theta, \omega, \beta) du$$

$$- \sum\limits_{j=1}^{M_i - d_i} \int\limits_{-\infty}^{\infty} \phi(u)\left[\frac{\omega^{1/2}S_{1i}(\beta)}{(d_i\theta + \omega)^2} + u\frac{\omega}{2\theta^{1/2}(d_i\theta + \omega)^{3/2}}\right]^2 h_{ij}'[u:\theta, \omega, \beta] P(u: \theta, \omega, \beta) du$$

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$$+ \sum_{j=1}^{M_i-d_i} \sum_{g=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) [\frac{\omega^{1/2} S_{1i}(\beta)}{(d_i\theta+\omega)^2} + u \frac{\omega}{2\theta^{1/2}(d_i\theta+\omega)^{3/2}}]^2 \, h_{ij}[u:\theta,\omega,\beta] \, h_{ig}[u:\theta,\omega,\beta] P(u:\theta,\omega,\beta) du$$

$$(A.15)$$

$$\frac{\partial^2 i_i(\theta,\omega,\beta)}{\partial\theta\partial\omega} = \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) [\frac{S_{1i}(\beta)(d_i\theta - 3\omega)}{2\omega^{1/2}(d_i\theta+\omega)^3} + u \frac{2d_i\theta-\omega}{4\theta^{1/2}(d_i\theta+\omega)^{5/2}}] \, h_{ij}[u:\theta,\omega,\beta] P(u:\theta,\omega,\beta) du$$

$$- \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) [\frac{\omega^{1/2} S_{1i}(\beta)}{(d_i\theta+\omega)^2} + u \frac{\omega}{2\theta^{1/2}(d_i\theta+\omega)^{3/2}}]$$

$$x[\frac{\ln[T_{ij}] - \beta^t Z_{ij}}{2\omega^{3/2}} - \frac{S_{1i}(\beta)(3\theta\omega+d_i\theta^2)}{2\omega^{3/2}(d_i\theta+\omega)^2} - u \frac{\theta^{1/2}}{2(d_i\theta+\omega)^{3/2}}] \, h_{ij}[u:\theta,\omega,\beta] P(u:\theta,\omega,\beta) du$$

$$+ \sum_{j=1}^{M_i-d_i} \sum_{g=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) [\frac{\ln[T_{ij}] - \beta^t Z_{ij}}{2\omega^{3/2}} - \frac{S_{1i}(\beta)(3\theta\omega+d_i\theta^2)}{2\omega^{3/2}(d_i\theta+\omega)^2} - u \frac{\theta^{1/2}}{2(d_i\theta+\omega)^{3/2}}]$$

$$x[\frac{\omega^{1/2} S_{1i}(\beta)}{(d_i\theta+\omega)^2} + u \frac{\omega}{2\theta^{1/2}(d_i\theta+\omega)^{3/2}}] \, h_{ij}[u:\theta,\omega,\beta] \, h_{ig}[u:\theta,\omega,\beta] P(u:\theta,\omega,\beta) du$$

$$(A.16)$$

$$\frac{\partial^2 i_i(\theta,\omega,\beta)}{\partial\theta\partial\beta_k} = - \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) [\frac{\omega^{1/2} [\sum_{j=1}^{M_i} \delta_{ij} Z_{ijk}]}{(d_i\theta+\omega)^2}] \, h_{ij}[\theta,\omega,\beta] P(u:\theta,\omega,\beta) du$$

$$- \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) [\frac{Z_{ijk}}{\omega^{1/2}} - \frac{\theta[\sum_{j=1}^{M_i} \delta_{ij} Z_{ijk}]}{\omega^{1/2}(d_i\theta+\omega)}][\frac{\omega^{1/2} S_{1i}(\beta)}{(d_i\theta+\omega)^2} + u \frac{\omega}{2\theta^{1/2}(d_i\theta+\omega)^{3/2}}] \, h_{ij}[u:\theta,\omega,\beta] P(u:\theta,\omega,) du$$

$$+ \sum_{j=1}^{M_i-d_i} \sum_{g=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) [\frac{\omega^{1/2} S_{1i}(\beta)}{(d_i\theta+\omega)^2} + u \frac{\omega}{2\theta^{1/2}(d_i\theta+\omega)^{3/2}}][\frac{Z_{ijk}}{\omega^{1/2}} - \frac{\theta[\sum_{j=1}^{M_i} \delta_{ij} Z_{ijk}]}{\omega^{1/2}(d_i\theta+\omega)}] \, h_{ij}[u:\theta,\omega,\beta]$$

$$x h_{ig}[u:\theta,\omega,\beta] P(u:\theta,\omega,\beta) du, \quad k=0,...,p \qquad (A.17)$$

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$$\frac{\partial^2 i_i(\theta,\omega,\beta)}{\partial\omega^2} = \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) \left[\frac{S_{1i}(\beta)(3d_i^2\theta^3+10d_i\theta^2\omega+15\theta\omega^2)}{4\omega^{5/2}(d_i\theta+\omega)^3} - \frac{3(\ln[T_{ij}] - \beta^t Z_{ij})}{4\omega^{5/2}}\right.$$

$$\left. +u \frac{3\theta^{1/2}}{4(d_i\theta+\omega)^{5/2}}\right] h_{ij}[u:\theta,\omega,\beta]P(u:\theta,\omega,\beta)du$$

$$- \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u)\left[\frac{\ln[T_{ij}] - \beta^t Z_{ij}}{2\omega^{3/2}} - \frac{S_{1i}(\beta)(3\theta\omega+d_i\theta^2)}{2\omega^{3/2}(d_i\theta+\omega)^2} - u\frac{\theta^{1/2}}{2(d_i\theta+\omega)^{3/2}}\right]^2 h_{ij}'[u:\theta,\omega,\beta]P(u:\theta,\omega,\beta)du$$

$$+ \sum_{j=1}^{M_i-d_i} \sum_{g=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u)\left[\frac{\ln[T_{ij}] - \beta^t Z_{ij}}{2\omega^{3/2}} - \frac{S_{1i}(\beta)(3\theta\omega+d_i\theta^2)}{2\omega^{3/2}(d_i\theta+\omega)^2} - u\frac{\theta^{1/2}}{2(d_i\theta+\omega)^{3/2}}\right]$$

$$\times\left[\frac{\ln[T_{ig}] - \beta^t Z_{ig}}{2\omega^{3/2}} - \frac{S_{1i}(\beta)(3\theta\omega+d_i\theta^2)}{2\omega^{3/2}(d_i\theta+\omega)^2} - u\frac{\theta^{1/2}}{2(d_i\theta+\omega)^{3/2}}\right] h_{ij}[u:\theta,\omega,\beta]\, h_{ig}[u:\theta,\omega,\beta]P(u:\theta,\omega,\beta)du$$

$$\tag{A.18}$$

$$\frac{\partial^2 i_i(\theta,\omega,\beta)}{\partial\omega\partial\beta_k} = \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u)\left[-\frac{Z_{ijk}}{2\omega^{3/2}} + \frac{(3\theta\omega+d_i\theta^2)[\sum_{j=1}^{M_i}\delta_{ij}Z_{ijk}]}{2\omega^{3/2}(d_i\theta+\omega)^2}\right] h_{ij}[u:\theta,\omega,\beta]P(u:\theta,\omega,\beta)du$$

$$- \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u)\left[\frac{Z_{ijk}}{\omega^{1/2}} - \frac{\theta[\sum_{j=1}^{M_i}\delta_{ij}Z_{ijk}]}{\omega^{1/2}(d_i\theta+\omega)}\right]\left[\frac{\ln[T_{ij}] - \beta^t Z_{ij}}{2\omega^{3/2}} - \frac{S_{1i}(\beta)(3\theta\omega+d_i\theta^2)}{2\omega^{3/2}(d_i\theta+\omega)^2} - u\frac{\theta^{1/2}}{2(d_i\theta+\omega)^{3/2}}\right]$$

$$\times h_{ij}'[u:\theta,\omega,\beta]P(u:\theta,\omega,\beta)du$$

$$+ \sum_{j=1}^{M_i-d_i} \sum_{g=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u)\left[\frac{\ln[T_{ij}] - \beta^t Z_{ij}}{2\omega^{3/2}} - \frac{S_{1i}(\beta)(3\theta\omega+d_i\theta^2)}{2\omega^{3/2}(d_i\theta+\omega)^2} - u\frac{\theta^{1/2}}{2(d_i\theta+\omega)^{3/2}}\right]$$

$$\times\left[\frac{Z_{igk}}{\omega^{1/2}} - \frac{\theta[\sum_{j=1}^{M_i}\delta_{ij}Z_{ijk}]}{\omega^{1/2}(d_i\theta+\omega)}\right] h_{ij}[u:\theta,\omega,\beta]\, h_{ig}[u:\theta,\omega,\beta]P(u:\theta,\omega,\beta)du \tag{A.19}$$

$$\frac{\partial^2 i_i(\theta,\omega,\beta)}{\partial\beta_k\partial\beta_{k'}} = -\sum_{j=1}^{M_i-d_i}\int_{-\infty}^{\infty}\phi(u)[\frac{Z_{ijk}}{\omega^{1/2}} - \frac{\theta\ [\sum_{j=1}^{M_i}\delta_{ij}Z_{ijk}]}{\omega^{1/2}(d_i\theta+\omega)}][\frac{Z_{ijk'}}{\omega^{1/2}} - \frac{\theta\ [\sum_{j=1}^{M_i}\delta_{ij}Z_{ijk'}]}{\omega^{1/2}(d_i\theta+\omega)}]$$

$$x\ h_{ij}'[u:\theta,\omega,\ \beta]P(u:\ \theta,\omega,\ \beta)du$$

$$+ \sum_{j=1}^{M_i-d_i}\sum_{g=1}^{M_i-d_i}\int_{-\infty}^{\infty}\phi(u)[\frac{Z_{ijk}}{\omega^{1/2}} - \frac{\theta\ [\sum_{j=1}^{M_i}\delta_{ij}Z_{ijk}]}{\omega^{1/2}(d_i\theta+\omega)}][\frac{Z_{igk'}}{\omega^{1/2}} - \frac{\theta\ [\sum_{j=1}^{M_i}\delta_{ij}Z_{ijk'}]}{\omega^{1/2}(d_i\theta+\omega)}]$$

$$x\ h_{ij}[u:\ \theta,\omega,\beta]\ h_{ig}[u:\ \theta,\omega,\beta]\ P(u:\ \theta,\omega,\ \beta)du,\ \ k,\ k'=0,...,p \tag{A.20}$$

Figure 1

Check Of Fit Of Multivariate Normal Model
Framingham Data
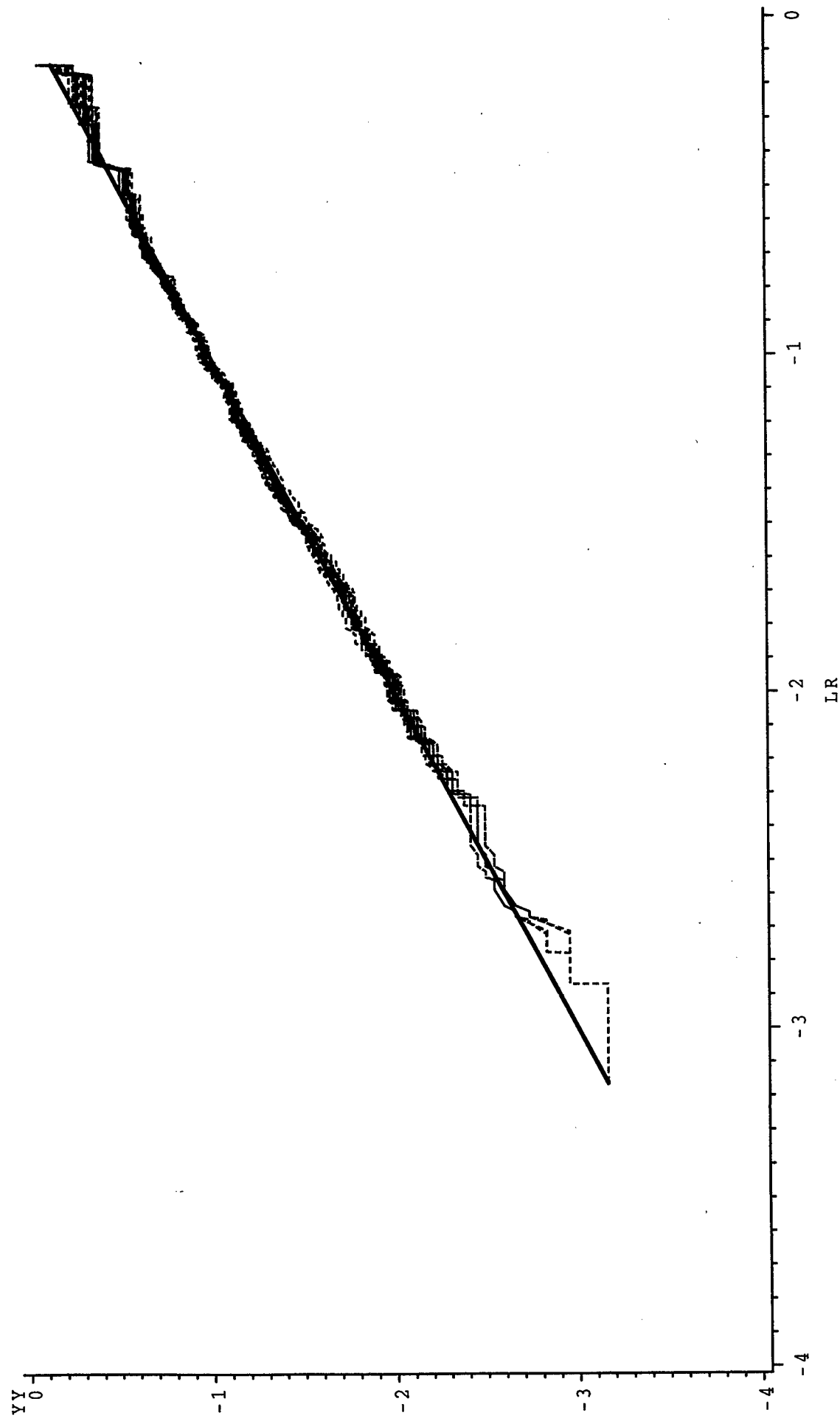
Figure 2

Check Of Fit Of Multivariate Normal Model
Litter—Matched Rats Data Set
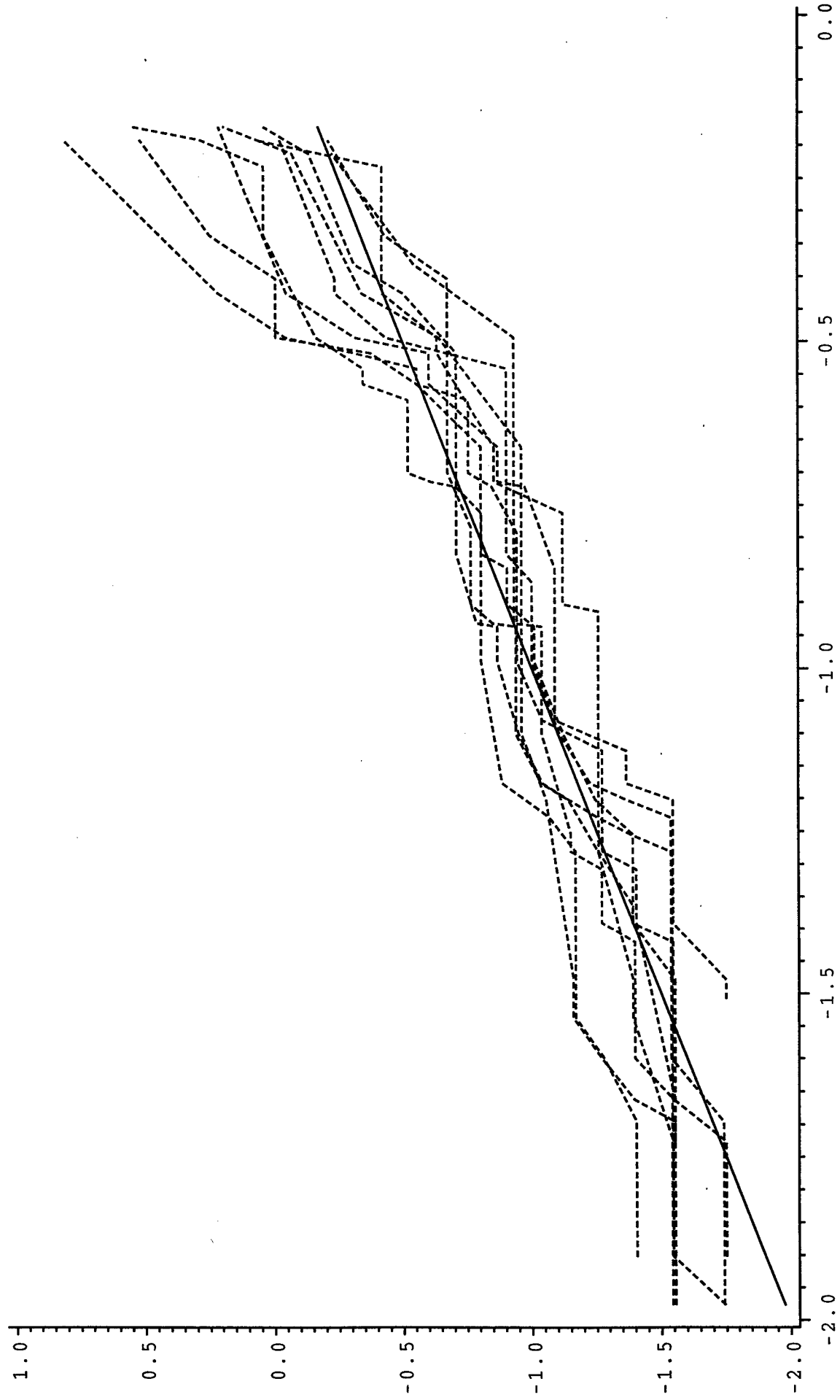
Figure 3
Check Of Fit Of Multivariate Normal Model
Skin—Graft Data Set
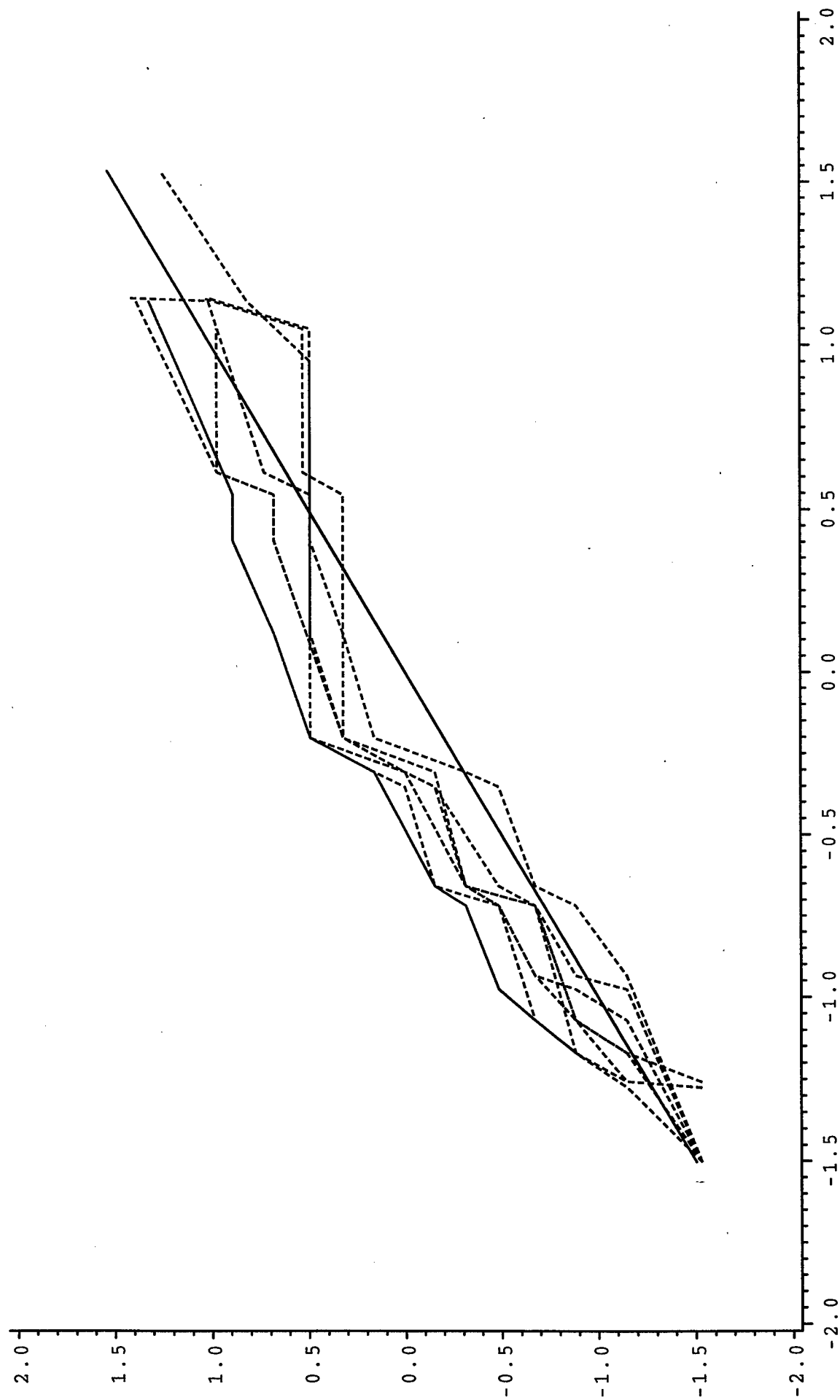
Joint Modeling of Death Times
and
Counts Using a Random Effects Model

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Abstract

We consider the problem of modeling count data where the observation period is determined by the survival time of the individual under study. We assume a random effects or frailty model to allow for a possible association between the death times and the counts. We assume that, given a random effect, the death times follow a Weibull distribution with a rate that depends on some covariates. For the counts, given the random effect, a Poisson process is assumed with the intensity depending on time and the covariates. A gamma model is assumed for the random effect. Maximum likelihood estimators of the model parameters are obtained. The model is applied to data set of patients with breast cancer who received a bone marrow transplant. A model for the time to death and the number of supportive transfusions a patient received is constructed and consequences of the model are examined.

1. INTRODUCTION

A common problem that arises in longitudinal studies is to model the effects of some explanatory factors on the number of occurrences of a given event that have occur in some time interval. For example, one may wish to model the number of transfusions given to a bone marrow transplant patient in the course of their recovery, the number of admissions to the hospital of a patient with a serious illness, or the number of doses of a drug given to a patient with a heart attack in the emergency room. We shall denote by $N(t)$ denote the cumulative number of events that have occurred up to time t.

Data on $N(t)$ is available only as long as the patient is under observation. Patients can be removed from the study in one of two ways. They can be removed alive or censored at either a random lost-to-follow-up time or at the end of the study, or, observation on the patient can stop due to the death of the patient. We shall let X denote the time to death and (T, δ) denote the on study time and censoring indicator ($\delta=1$ if $T=X$, $\delta=0$ if $T>X$). We assume that the censoring mechanism is independent of the time to death and the number of events that have occurred at a given time.

In most cases it is not reasonable to assume that $N(t)$ and T are independent. In the bone marrow examples, patients who require more frequent blood transfusions are often having problems in maintaining their graft and as such are at higher risk for death than patients requiring fewer transfusions. Thus $N(t)$ and X should be positively associated. We shall induce an association between the counts and the survival times by using a so called shared frailty or random effect model. Frailty models have been used to model association in survival studies by a number of authors (See, for example Clayton 1978, Nielsen et al 1992, Klein 1992). Lawless (1987) has used random effects models to model count data. Here we shall introduce a common random effect in the model for T and $N(t)$ which induces a positive association between these two random quantities. The random effect represents the unmeasured factors that are acting simultaneously on both the number of events and the time to death. The variance of this random factor represents a measure of the strength of this positive association between the two random quantities.

In the next Section we will describe how a model using a common gamma frailty can be applied in this problem. We shall assume that, conditional on a set of potential risk factors, the time to death follows a Weibull distribution and the counts follow a Poisson process. We develop some properties of the model which help in the interpretation of the effects of the covariates on both the time to death and the number of events. In Section 3 we discuss the problem of estimating model parameters.

In Section 4 we apply these procedures to data from the Autologous Blood and Marrow Transplant Registry (ABMTR) on 701 patients with high risk breast cancer given high dose

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chemotherapy followed by autologous hematopoietic stem-cell support (an autologous bone marrow transplant). Patients were transplanted between 1990-1994 and followed until 1996. The median follow up time was 16.5 months with a range of 0.1 to 66 months. Three hundred and sixty-one (51.5%) of the patients died during the course of the study. Patients had median of 5 transfusions from the same donor. One hundred and forty-four requiring no transfusions and the maximum number of transfusions was 172. Table 1 summarizes the number of transfusions.

Table 1
Frequency of transfusions

Number of Transfusions	Number of patients
0	144
1	30
2	63
3	53
4	45
5	34
6	31
7	24
8	22
9	21
10	19
11	8
12	16
13	13
14	10
15	9
16	11
17	9
18	13
19	8
≥ 20	118

Five potential risk factors were considered in the study. Two factors were treated as continuous covariates: patient's age at transplant (median 44 years range 24.5-64.4) and the waiting time from diagnosis to transplant (median 626 days range 92 to 4811 days). One factor, year of transplant was coded as a binary covariate (90-92 (44%) and 93-94 (56%)). Two factors were categorical and coded as a series of binary covariates: Stage of disease at transplant (primary stage 2-3 disease (32.2%), metastatic disease in complete remission (18.7%), partial remission (28.0%) or resistant disease (21.1 %)) and the graft source (bone marrow (49.4%), peripheral blood stem cell (39.5%), or both (11.1%)). Additional details of the study can be found in Antman et al (1997).

2. The Model

In this Section we present a model for the joint distribution of the time to death, X, and the number of events which occur up to time t, N(t). We let W denote a shared random effect which has a common multiplicative effect on both the rate at which death is occurring and the rate at which the events are occurring. This random effect, which is allowed to vary from person to person, is analogous to a frailty in the usual multivariate survival modeling (See Klein et al (1992)) and as a memodel for unobserved heterogeneity in modeling count data (See Lawless (1987)). It represents common genetic, disease specific or environmental factors that were not measured on the patient which are affecting both the number of events and the time to death. Here we assume that W has a gamma distribution with a mean of 1 and a variance θ. That is ,

$$f(w) = \frac{w^{1/\theta - 1} \exp[-w/\theta]}{\Gamma[1/\theta]\, \theta^{1/\theta}} , \; \theta \geq 0 \qquad (2.1)$$

For a given patient we have two sets of covariates which are potential explanatory factors for either the time to death or for the count (or both). Suppose that there are p_d covariates which are explanatory for death and p_c covariates which are explanatory for the number of events. We define the $p_d + 1$ vector $\mathbf{Z_d}$ whose first component is equal to 1 and whose remaining p_d columns are set equal to the p_d explanatory covariates for death. Similarly let $\mathbf{Z_c}$ be the $p_c + 1$ vector of risk factor for the number of events. Again for connivance the first component of $\mathbf{Z_c}$ is set to 1 for an intercept term. Note that the same factor can be included in both $\mathbf{Z_p}$ and $\mathbf{Z_c}$.

Given the value of W=w (and $\mathbf{Z_d}$) we assume that the time to death follows a Weibull distribution with hazard rate

$$h(t \mid \mathbf{Z_d}) = w\alpha t^{\alpha-1} \exp\{\beta \mathbf{Z_d}\} , \; t \geq 0, \, \alpha > 0. \qquad (2.2)$$

This is a standard Weibull regression model as discussed in Klein and Moeschberger (1997) with the inclusion of the random effect, w.

For the number of events we assume, given W=w (and $\mathbf{Z_c}$), that N(t) follows a Poisson process with a rate

$$\lambda(t \mid \mathbf{Z_c}) = w t^{\phi} \exp\{\gamma \mathbf{Z_c}\}, \; t \geq 0, \, \phi > 0. \qquad (2.3)$$

Given W we assume that N(t) and X are independent.

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To study properties of this model we first need to note that $N(t)$ is only observable as long as $t \leq X$, and that $N(t)=N(X)$ when $X>t$. Thus we have, given $W=w$, that, with some abuse of notation,

$$
\begin{aligned}
P[X=t, N(s)=k|w] &= P[X=t, N(\min(s,t))=k|w] \\
&= w\alpha t^{\alpha-1} \exp\{\beta Z_d\}\exp[-wt^\alpha \exp\{\beta Z_d\}] \\
&\quad \times \frac{[w\min(s,t)^\phi\exp\{\gamma Z_c\}]^k \exp[-w\min(s,t)^\phi\exp\{\gamma Z_c\}]}{k!} \quad . \quad (2.4)
\end{aligned}
$$

Also

$$
\begin{aligned}
P[X\geq t, N[s]=k \,|w] &= \int_t^\infty P[X = t, N[s]=k \,|w] \, dt \text{ for } t \geq s \\
&= \int_t^s P[X = t, N[t]=k \,|w] \, dt + P[X\geq s, N[s]=k \,|w] \text{ for } t<s. \quad (2.5)
\end{aligned}
$$

To find the unconditional distribution of X and $N(\cdot)$ we take the expectation of (2.4) with respect W. For $\theta>0$, this yields,

$$
\begin{aligned}
P[X=t, N(s)=k] &= \int_0^\infty P[X=t, N(s)=k|w] \, \frac{w^{1/\theta-1}\exp[-w/\theta]}{\Gamma[1/\theta] \, \theta^{1/\theta}} \, dw \\[2mm]
&= \frac{\Gamma(1/\theta+k+1)}{k! \, \Gamma(1/\theta)} [\alpha\theta t^{\alpha-1} \exp\{\beta Z_d\}] [\theta\min(s,t)^\phi\exp\{\gamma Z_c\}]^k \quad (2.6) \\
&\quad \times [1+\theta \, t^\alpha \exp\{\beta Z_d\}+\theta \, \min(s,t)^\phi\exp\{\gamma Z_c\}]^{-(1/\theta+k+1)}.
\end{aligned}
$$

When θ is equal to zero then W is equal to one almost surely and X and $N(\cdot)$ are independent Weibull and Poisson random variables, respectively.

From (2.5) we have

$$
P[X\geq t, N(s)=k] = \frac{\Gamma(1/\theta+k)}{k! \, \Gamma(1/\theta)} [\theta s^\phi\exp\{\gamma Z_c\}]^k [1+\theta \, t^\alpha \exp\{\beta Z_d\}+\theta \, s^\phi\exp\{\gamma Z_c\}]^{-(1/\theta+k)},
$$

$$(2.7)$$

when $t \geq s$ and

$$
\begin{aligned}
P[X\geq t, N(s)=k] &= \frac{\Gamma(1/\theta+k+1)}{k! \, \Gamma(1/\theta)} [\alpha\theta^{k+1} \exp\{\beta Z_d+k\gamma Z_c\}] \\
&\quad \times \int_t^s u^{k\phi+\alpha-1} \{1+\theta u^\alpha\exp\{\beta Z_d\}+\theta u^\phi\exp\{\gamma Z_c\} \}^{-(1/\theta+k+1)}du \quad (2.8)
\end{aligned}
$$

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$$+\frac{\Gamma(1/\theta+k)}{k!\ \Gamma(1/\theta)}\ [\theta s^{\phi}\exp\{\gamma Z_c\}]^k\ [1+\theta\ s^{\alpha}\ \exp\{\beta Z_d\}+\theta\ s^{\phi}\exp\{\gamma Z_c\}]^{-(1/\theta+k)},$$

when s>t.

For this model one can show that the marginal distribution of X is a univariate Burr distribution with survival function

$$S(t) = [1+\theta\ t^{\alpha}\ \exp\{\beta Z_d\}]^{-1/\theta}. \tag{2.9}$$

For s≤t the conditional distribution of N(s) given X >t follows a Pascal distribution with parameters 1/θ and q with

$$q=\frac{\theta\ s^{\phi}\exp\{\gamma Z_c\}}{1+\theta t^{\alpha}\exp\{\beta Z_d\}+\theta s^{\phi}\exp\{\gamma Z_c\}}. \tag{2.10}$$

That is

$$P[N(s)=k\ |T>t] = \binom{1/\theta+k-1}{k}\ q^k p^{1/\theta}, \tag{2.11}$$

where p=1-q. The mean number of transfusions at time s for a patient alive at time t≥s is $E[N(s)=k\ |T>t] = q/(\theta p)$ and the conditional variance is $V[N(s)=k\ |T>t] =q/(\theta p^2)$.

To find the marginal distribution of N(s) we need to compute $P[X\geq 0, N(s)=k]$. From (2.8) we see that

$$P[N(s)=k] =\frac{\Gamma(1/\theta+k+1)}{k!\ \Gamma(1/\theta)}\ [\alpha\theta^{k+1}\ \exp\{\beta Z_d+k\gamma Z_c\}]$$

$$x\int_0^s u^{k\phi+\alpha-1}\ \{1+\theta u^{\alpha}\exp\{\beta Z_d\}+\theta u^{\phi}\exp\{\gamma Z_c\}\ \}^{-(1/\theta+k+1)}du \tag{2.12}$$

$$+\frac{\Gamma(1/\theta+k)}{k!\ \Gamma(1/\theta)}\ [\theta s^{\phi}\exp\{\gamma Z_c\}]^k\ [1+\theta\ s^{\alpha}\ \exp\{\beta Z_d\}+\theta\ s^{\phi}\exp\{\gamma Z_c\}]^{-(1/\theta+k)}.$$

This quanity needs to be evaluated numerically.

3. Estimation of model parameters

Estimation of model parameters is based on the total number of transfusions a patient recieved during their period of observation. Let T_i be the on study time for the ith person and δ_i be the death indicator (δ_i =1 if dead, δ_i =0 if censored). Let $N_i = N_i(T_i)$ be the total number of transfusion given to the patient. Note that, as opposed to Lawless (1987), we only know the total number of events an individual has experienced not the exact times at which these events have occurred. Let Z_{di} and Z_{ci} be the covariate vectors for the ith person. For individuals who die, their contribution to the likelihood is $P[X=T_i, N(T_i)=N_i]$ which is given by (2.6). For individuals

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who are censored, their contribution to the likelihood is $P[X>T_i, N(T_i)=N_i]$, which is given by (2.7). Based on a sample of size n, the log likelihood is (up to an additive constant) given by

$$LL= \sum_{i=1}^{n} \left\{ \ln[\Gamma(1/\theta+N_i+\delta_i)] +\delta_i\ln[\alpha] + [\delta_i (\alpha-1) +N_i\phi] \ln[T_i]+ \delta_i \beta Z_{di} + N_i\gamma Z_{ci} +(N_i+\delta_i)\ln[\theta] \right.$$
$$\left. - (1/\theta+N_i +\delta_i) \ln[1+\theta T_i^{\alpha}\exp\{\beta Z_{di}\}+\theta T_i^{\phi}\exp\{\gamma Z_{ci}\}] \right\} -n \ln[\Gamma(1/\theta)], \qquad (3.1)$$

when $\theta>0$. For $\theta=0$ the log likelihood is the sum of two likelihoods, $L_1(\alpha, \beta)$ and $L_2(\phi, \gamma)$, the first the usual likelihood from a Weibull regression model,

$$L_1(\alpha, \beta)= \sum_{i=1}^{n} \delta_i[(\alpha-1) \ln[T_i] + \ln[\alpha] + \beta Z_{di}] - T_i^{\alpha} \exp\{\beta Z_{di} \}$$

and the second Poisson likelihood,

$$L_2(\phi, \gamma) = \sum_{i=1}^{n} N_i[\phi \ln[T_i] + \gamma Z_{ci}] - T_i^{\phi} \exp\{\gamma Z_{ci} \}.$$

Estimates of $\theta, \alpha, \phi, \beta$ and γ are found by maximizing the log likelihood numerically. In the appendix we provide the score statistics, which are the first partial derivatives of LL with respect to the parameters, and the observed information matrix, **I**, which is the negative of the matrix of second partial derivatives. The inverse of the observed information matrix is the estimated covariance matrix of the maximum likelihood estimators. Wald, score and likelihood ratio tests for the parameters of the model can be performed using standard constructions (See Appendix B of Klein and Moeschberger (1997) for details.)

4. Example

We shall illustrate inference for this model using the data discussed in Section 1. To estimate model parameters we used Marquart's (1963) method to numerically maximize the likelihood (3.1). This method, which a compromise between the method of steepest descent and the Newton-Raphson technique, was used since it is difficult to obtain initial estimates of the model parameters, and the number of parameters is quite large. Details of the technique are found in Appendix A of Klein and Moeschberger (1997). A FORTRAN program was written to perform the estimation procedures.

We first fit the model with all 5 factors for both the time to death and the number of transfusions. In Table 2 we report the parameter estimates, standard errors and the Wald chi-square test of the hypothesis the parameter is equal to zero. We then use a backward stepwise procedure

to eliminate factors one at time to find a final model in which all factors are significant at the 5% level.

The final model is reported in Table 3. Here we see that the risk factors for death are the stage of disease with patients transplanted with resistant disease or in partial remission having higher death rates; the source of the graft, with patients transplanted with both bone marrow and peripheral blood stem cells having a worst prognosis; and the lag time between diagnosis and transplant with patients being transplanted soon after diagnosis doing more poorly. For the number of transfusions, all five factors are significant. Here younger patients transplanted later than 1992 with a long time from diagnosis to transplant tend to have fewer transfusions. For stage of disease patients transplanted in complete remission or with resistant disease tend to have more transfusions, while patients given only peripheral blood stem cells tend to have fewer transfusions.

The Wald test of the hypothesis of no association between the death times and the number of transfusions (i.e. H_0: $\theta=0$) is strongly rejected in both models. Since this is a test about a parameter on the boundary of the parameter space, the likelihood ratio test may be more appropriate. When $\theta=0$, X and N[·] are independent, so the likelihood is the product of the typical Weibull likelihood and a Poisson likelihood. Maximum likelihood estimates can be found by maximizing these two likelihoods separately. The total log likelihood is the sum of two individual likelihoods. Table 4 shows the results of fitting the two separate models, using the covariates in the final model. Here the total likelihood is -8049.86 which yields a likelihood ratio chi-square of 7,879.20 with 1 degree of freedom, which is highly significant.

A comparison of Tables 3 and 4 shows that effect of ignoring the significant association between the death times and the number of transfusions. In the models for the death times, the factor graft source is not significant in the independence model, but is highly significant in the dependence model. In the models for the number of transfusions the two models are also different. First, the baseline intensity, $t^\phi \exp\{\beta_0\}$ is decreasing in the independence model ($\phi = -0.18$), but increasing in time in the dependence model ($\phi = 0.40$). Second, the sign of the regression coefficient for "partial remission" is different in the two model.

There are several implications of the model which can be deducted from the results in Section 2. First we can estimate the mean number of transfusions at time t for a patient who is alive at this time with a given set of covariates by $\hat{q}/(\hat{\theta} \hat{p})$, with q given by (2.10). A routine use of the delta method gives an estimate of the standard error of the estimate. Using (2.11) we can estimate the probability that a patient will have k transfusions by time s given they are alive at this time. Again, standard errors can be found by a simple application of the delta method. Table 5 -show the point estimates and standard errors of these two quantities for a 44 year old patient transplanted after 1992 with a 626 day waiting time from diagnosis to transplant. Estimates at 6,

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12, 18 and 24 months are given for all twelve combinations of disease status and cell source. Here we see that for patients not having resistant disease the expected number of transfusions varies from about 3.5-4 for patients given peripheral blood stem cells only, from about 5-6 for patients given bone marrow only, and from about 5-8 for patients given both types of cells. Patients with resistant disease are expected to have substantially more transfusions. Similar patterns hold for the estimated probabilities of at least one transfusion. Note that for a fixed set of covariates the expected number of transfusions is not necessarily increasing in time since this is the expected number of transfusions for a survivor and patients with more transfusions in most cases tend to have a lower survival rate.

The model can also be used to examine how the number of transfusions a patient has effects their survival rates. Using the parameter estimates and (2.11) one can estimate the marginal probability, given the covariates, that $N(s)=k$. The integral in (2.11) needs to be evaluated numerically, which we do in the sequel using a 24 point Gauss Legendre formula. Using this estimate and (2.7) we can estimate the conditional survival function for an individual alive at time s who has had a given number of transfusions. That is we estimate $P[X>t \mid N[s]=k, X \geq s, Z_d, Z_c]$. Figure 1 shows the effect of the number of transplants on survival for a 44 year old patient with primary disease transplanted using bone marrow after 1992 with a 626 day waiting time from diagnosis to transplant who was alive with 0, 1, 2 ,5, 10, or 15 transfusions at 6 months. We see that after 3 years from this time the estimated survival ranges from about 98% for a patient give no transfusions to about 32% for a patient given 15 transfusions. To study the effect of the risk factors on survival we plot in Figure 2 the conditional survival curves for the twelve combinations of graft source and disease status for a 44 year old patient transplanted after 1992 with a 626 day waiting time from diagnosis to transplant who was alive with 5 transfusions at 6 months.

Acknowledgments

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Table 2
Maximum Likelihood Estimates Of Model Parameters In Inital Model

Factor	Estimate	SE	D.F.	Wald X^2	p-value
Time to Death					
Intercept	-5.94	0.50			
Stage Of Disease			3	121.52	<0.0001
Complete Remission	0.63	0.24	1	6.89	0.0087
Partial Remission	2.10	0.22	1	91.12	<0.0001
Resistant Disease	2.15	0.24	1	80.25	<0.0001
Graft Source			2	10.59	0.0050
Peripheral Blood Stem Cell	-0.01	0.18	1	0.03	0.8625
Marrow And Peripheral Blood	0.78	0.26	1	9.00	0.0027
Year Of Transplant (90-92)	0.15	0.17	1	0.77	0.3807
Age	0.01	0.01	1	2.09	0.1481
Waiting Time To Transplant	-2.3×10^{-4}	6.8×10^{-5}	1	11.12	0.0009
Number of Transfusions					
Intercept	0.47	0.35			
Stage Of Disease			3	53.21	<0.0001
Complete Remission	3.2×10^{-3}	0.15	1	4.6×10^{-4}	0.9829
Partial Remission	0.26	0.14	1	3.45	0.0633
Resistant Disease	1.03	0.15	1	47.15	<0.0001
Graft Source			2	20.72	<0.0001
Peripheral Blood Stem Cell	-0.35	0.12	1	8.51	0.0035
Marrow And Peripheral Blood	0.37	0.19	1	3.79	0.0515
Year Of Transplant (90-92)	-0.26	0.12	1	4.73	0.0296
Age	0.02	0.01	1	11.72	0.0006
Waiting Time To Transplant	-7.6×10^{-5}	3.2×10^{-5}	1	5.78	0.0162
θ	1.58	0.10	1	263.01	<0.0001
α	1.31	0.06			
ϕ	0.41	0.05			
Log Likelihood	-4108.86				

Table 3
Maximum Likelihood Estimates Of Model Parameters In Final Model

Factor	Estimate	SE	D.F.	Wald X^2	p-value
Time to Death					
Intercept	-5.23	0.245			
Stage Of Disease			3	125.27	<0.0001
Complete Remission	0.65	0.240	1	7.34	0.0068
Partial Remission	2.09	0.220	1	90.25	<0.0001
Resistant Disease	2.21	0.234	1	89.20	<0.0001
Graft Source			2	9.91	0.0070
Peripheral Blood Stem Cell	-0.05	0.168	1	0.09	0.7660
Marrow And Peripheral Blood	0.71	0.249	1	8.13	0.0044
Waiting Time To Transplant	-2.2×10^{-4}	6.8×10^5	1	10.31	0.0013
Number of Transfusions					
Intercept	0.79	0.286			
Stage Of Disease			3	57.41	<0.0001
Complete Remission	0.02	0.146	1	0.02	0.8875
Partial Remission	0.25	0.141	1	3.14	0.0762
Resistant Disease	1.05	0.152	1	47.72	<0.0001
Graft Source			2	21.82	<0.0001
Peripheral Blood Stem Cell	-0.38	0.118	1	10.37	0.0013
Marrow And Peripheral Blood	0.35	0.182	1	3.70	0.0545
Year Of Transplant (90-92)	-0.32	0.088	1	13.69	0.0002
Age	.02	0.005	1	10.58	0.0011
Waiting Time To Transplant	-7.2×10^{-5}	3.2×10^{-5}	1	5.11	0.0238
θ	1.57	0.097	1	267.46	<0.0001
α	1.31	0.057	1		
ϕ	0.40	0.050			
Log Likelihood	-4110.26				

Table 4
Model Based On Independence Between The Death Times And Number Of Transfusions

	Estimate Time to Death	SE	D.F.	Wald X^2	p-value
Intercept	-4.54	0.21			
Stage Of Disease			3	122.174	<0.0001
Complete Remission	0.67	0.19	1	12.06	0.0005
Partial Remission	1.53	0.17	1	79.73	<0.0001
Resistant Disease	1.76	0.18	1	100.06	<0.0001
Graft Source			2	3.44	0.1787
Peripheral Blood Stem Cell	-0.17	0.12	1	2.17	0.1407
Marrow And Peripheral Blood	0.30	0.17	1	3.03	0.0820
Waiting Time To Transplant	-1.84×10^{-4}	5.94×10^{-5}	1	9.61	0.0019
α	1.04	0.05			
Weibull Log Likelihood	-1599.32				

Number of Transfusions

	Estimate	SE	D.F.	Wald X^2	p-value
Intercept	2.39	0.08			
Stage Of Disease			3	801.60	<0.0001
Complete Remission	-0.04	0.04	1	1.42	0.2338
Partial Remission	-0.27	0.04	1	55.87	<0.0001
Resistant Disease	0.58	0.03	1	304.15	<0.0001
Graft Source			2	236.31	<0.0001
Peripheral Blood Stem Cell	-0.37	0.03	1	180.97	<0.0001
Marrow And Peripheral Blood	0.05	0.03	1	1.70	0.1924
Year Of Transplant (90-92)	-0.12	0.02	1	23.73	<0.0001
Age	0.01	1.51E-03	1	83.61	<0.0001
Waiting Time To Transplant	-3.23E-05	1.20E-05	1	7.20	0.0073
ϕ	-0.18	0.01			
Poisson Log Likelihood	-6450.54				
Total Log Likelihood	-8049.86				

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Table 5
Estimated Mean Number Of Transfusions And The Probability Of At Least One Transfusion For A 44 Year Old Patient Transplanted After 1992 With A 626 Day Waiting Time To Transplant For A Patient Alive at 6, 12, 18 or 24 Months

Disease Status[1]	Cell Source[2]	Expected Number Of Transfusions /SE				Probability Of At Least One Transfusion/SE			
		6 months	12 months	18 months	24 months	6 months	12 months	18 months	24 months
Primary	BM	5.946	7.087	7.486	7.546	0.774	0.795	0.802	0.803
		0.628	0.647	0.649	0.650	0.024	0.021	0.021	0.021
CR	BM	5.671	6.281	6.216	5.929	0.767	0.781	0.779	0.773
		0.688	0.654	0.615	0.588	0.026	0.024	0.025	0.026
PR	BM	5.082	4.266	3.513	2.956	0.752	0.727	0.696	0.667
		0.480	0.410	0.365	0.329	0.026	0.031	0.036	0.041
Resistant	BM	10.780	8.810	7.157	5.975	0.840	0.820	0.797	0.774
		1.150	0.948	0.830	0.739	0.023	0.028	0.034	0.039
Primary	PBSC	4.085	4.890	5.188	5.250	0.720	0.747	0.755	0.757
		0.555	0.607	0.618	0.616	0.029	0.025	0.025	0.025
CR	PBSC	3.907	4.358	4.338	4.158	0.713	0.730	0.729	0.723
		0.537	0.537	0.520	0.506	0.030	0.027	0.028	0.029
PR	PBSC	3.547	3.012	2.496	2.108	0.698	0.671	0.637	0.605
		0.375	0.323	0.286	0.257	0.028	0.033	0.038	0.042
Resistant	PBSC	7.536	6.230	5.091	4.265	0.803	0.780	0.753	0.727
		0.759	0.638	0.562	0.504	0.024	0.030	0.035	0.040
Primary	Both	7.851	8.617	8.462	8.023	0.807	0.818	0.816	0.810
		1.278	1.306	1.259	1.210	0.025	0.024	0.025	0.027
CR	Both	7.099	6.975	6.308	5.632	0.796	0.793	0.781	0.766
		1.201	1.106	1.025	0.959	0.027	0.028	0.031	0.035
PR	Both	5.153	3.710	2.843	2.299	0.754	0.705	0.660	0.622
		0.800	0.629	0.515	0.435	0.033	0.043	0.052	0.058
Resistant	Both	10.703	7.528	5.714	4.598	0.840	0.802	0.768	0.738
		1.513	1.160	0.939	0.790	0.027	0.037	0.046	0.053

[1] Primary - Primary Stage 2-3 disease; CR-Complete Remission; PR-Partial Remission; Resistant-Resistant disease.

[2] BM-Bone Marrow; PBSC- Peripheral Blood Stem Cells; Both- Both sources

Appendix

From (3.1) we have a log likelihood given by

$$LL = \sum_{i=1}^{n} \log[\Gamma(1/\theta + \delta_i + N_i)] + \ln[\alpha]\, D + (\alpha-1)\, S_{DLT} + \sum_{i=1}^{n} \delta_i\, \beta \mathbf{Z_{di}}$$

$$+\phi\, S_{NLT} + \sum_{i=1}^{n} N_i\, \gamma \mathbf{Z_{ci}} - \sum_{i=1}^{n} (1/\theta + \delta_i + N_i)\ln[Y_i] - (n/\theta)\ln[\theta] - n\ln[\Gamma(1/\theta)] \quad (A.1)$$

where D is the number of deaths, $S_{DLT} = \sum_{i=1}^{n} \delta_i \ln[T_i]$, $S_{NLT} = \sum_{i=1}^{n} N_i \ln[T_i]$, and

$Y_i = 1/\theta + T_i^{\alpha}\exp\{\beta \mathbf{Z_{di}}\} + T_i^{\phi}\exp\{\gamma \mathbf{Z_{ci}}\}$.

The score statistics are:

$$\frac{\partial LL}{\partial \alpha} = D/\alpha + S_{DLT} - \sum_{i=1}^{n} (1/\theta + \delta_i + N_i)\frac{\ln[T_i]\, T_i^{\alpha}\exp\{\beta \mathbf{Z_{di}}\}}{Y_i}; \quad (A.2)$$

$$\frac{\partial LL}{\partial \phi} = S_{NLT} - \sum_{i=1}^{n} (1/\theta + \delta_i + N_i)\frac{\ln[T_i]\, T_i^{\phi}\exp\{\gamma \mathbf{Z_{ci}}\}}{Y_i}; \quad (A.3)$$

$$\frac{\partial LL}{\partial \theta} = -\frac{1}{\theta^2}\sum_{i=1}^{n}\Psi(1/\theta + \delta_i + N_i) + \frac{1}{\theta^2}\sum_{i=1}^{n}\ln[Y_i] + \frac{1}{\theta^2}\sum_{i=1}^{n}\frac{1/\theta + \delta_i + N_i}{Y_i} + \frac{n}{\theta^2}[\ln[\theta] - 1 + \Psi(1/\theta)]; \quad (A.4)$$

$$\frac{\partial LL}{\partial \beta_j} = \sum_{i=1}^{n} \delta_i\, Z_{dij} - \sum_{i=1}^{n} (1/\theta + \delta_i + N_i)\frac{Z_{dij}\, T_i^{\alpha}\exp\{\beta \mathbf{Z_{di}}\}}{Y_i}, \quad j = 0,\ldots,p_d; \quad (A.5)$$

$$\frac{\partial LL}{\partial \gamma_j} = \sum_{i=1}^{n} N_i\, Z_{cij} - \sum_{i=1}^{n} (1/\theta + \delta_i + N_i)\frac{Z_{cij}\, T_i^{\phi}\exp\{\gamma \mathbf{Z_{ci}}\}}{Y_i}, \quad j = 0,\ldots,p_c, \quad (A.6)$$

where $\Psi(\cdot)$ is the digamma function.

The second partial derivaives of the log likelihood are:

$$\frac{\partial^2 LL}{\partial \alpha^2} = -D/\alpha^2 - \sum_{i=1}^{n} (1/\theta + \delta_i + N_i)\frac{(\ln[T_i])^2\, T_i^{\alpha}\exp\{\beta \mathbf{Z_{di}}\}[1/\theta + T_i^{\phi}\exp\{\gamma \mathbf{Z_{ci}}\}]}{Y_i^2}; \quad (A.7)$$

$$\frac{\partial^2 LL}{\partial \alpha \partial \phi} = \sum_{i=1}^{n} (1/\theta + \delta_i + N_i)\frac{(\ln[T_i])^2\, T_i^{\alpha}\exp\{\beta \mathbf{Z_{di}}\}T_i^{\phi}\exp\{\gamma \mathbf{Z_{ci}}\}}{Y_i^2}; \quad (A.8)$$

$$\frac{\partial^2 LL}{\partial\alpha\partial\theta}=\frac{1}{\theta^2}\sum_{i=1}^{n}\frac{\ln[T_i]\,T_i^{\alpha}\exp\{\beta Z_{di}\}}{Y_i}-\frac{1}{\theta^2}\sum_{i=1}^{n}(1/\theta+\delta_i+N_i)\frac{\ln[T_i]\,T_i^{\alpha}\exp\{\beta Z_{di}\}}{Y_i^2}; \quad (A.9)$$

$$\frac{\partial^2 LL}{\partial\alpha\partial\beta_j}=-\sum_{i=1}^{n}(1/\theta+\delta_i+N_i)\frac{\ln[T_i]Z_{dij}T_i^{\alpha}\exp\{\beta Z_{di}\}[1/\theta+T_i^{\phi}\exp\{\gamma Z_{ci}\}]}{Y_i^2}, \quad j=0,...,p_d; \quad (A.10)$$

$$\frac{\partial^2 LL}{\partial\alpha\partial\gamma_j}=\sum_{i=1}^{n}(1/\theta+\delta_i+N_i)\frac{\ln[T_i]Z_{cij}T_i^{\alpha}\exp\{\beta Z_{di}\}T_i^{\phi}\exp\{\gamma Z_{ci}\}]}{Y_i^2}, \quad j=0,...,p_c; \quad (A.11)$$

$$\frac{\partial^2 LL}{\partial\phi^2}=-\sum_{i=1}^{n}(1/\theta+\delta_i+N_i)\frac{(\ln[T_i])^2\,T_i^{\phi}\exp\{\gamma Z_{ci}\}[1/\theta+T_i^{\alpha}\exp\{\beta Z_{ci}\}]}{Y_i^2}; \quad (A.12)$$

$$\frac{\partial^2 LL}{\partial\phi\partial\theta}=\frac{1}{\theta^2}\sum_{i=1}^{n}\frac{\ln[T_i]\,T_i^{\phi}\exp\{\gamma Z_{ci}\}}{Y_i}-\frac{1}{\theta^2}\sum_{i=1}^{n}(1/\theta+\delta_i+N_i)\frac{\ln[T_i]\,T_i^{\phi}\exp\{\gamma Z_{di}\}}{Y_i^2}; \quad (A.13)$$

$$\frac{\partial^2 LL}{\partial\phi\partial\beta_j}=\sum_{i=1}^{n}(1/\theta+\delta_i+N_i)\frac{\ln[T_i]Z_{dij}T_i^{\alpha}\exp\{\beta Z_{di}\}T_i^{\phi}\exp\{\gamma Z_{ci}\}]}{Y_i^2}, \quad j=0,...,p_d; \quad (A.14)$$

$$\frac{\partial^2 LL}{\partial\phi\partial\gamma_j}=-\sum_{i=1}^{n}(1/\theta+\delta_i+N_i)\frac{\ln[T_i]Z_{cij}T_i^{\phi}\exp\{\gamma Z_{ci}\}[1/\theta+T_i^{\alpha}\exp\{\beta Z_{di}\}]}{Y_i^2}, \quad j=0,...,p_c; \quad (A.15)$$

$$\frac{\partial^2 LL}{\partial\theta^2}=\frac{2}{\theta^3}\sum_{i=1}^{n}\Psi(1/\theta+\delta_i+N_i)-\frac{2}{\theta^3}\sum_{i=1}^{n}\ln[Y_i]-\frac{2}{\theta^3}\sum_{i=1}^{n}\frac{1/\theta+\delta_i+N_i}{Y_i} \quad (A.16)$$
$$+\frac{1}{\theta^4}\sum_{i=1}^{n}\{\Psi'(1/\theta+\delta_i+N_i)-\frac{1}{Y_i}[2-\frac{1/\theta+\delta_i+N_i}{Y_i}]\}+\frac{n}{\theta^3}[3-2\ln[\theta]-2\Psi(1/\theta)-\frac{1}{\theta}\Psi'(1/\theta)];$$

$$\frac{\partial^2 LL}{\partial\theta\partial\beta_j}=\frac{1}{\theta^2}\sum_{i=1}^{n}\frac{Z_{dij}T_i^{\alpha}\exp\{\beta Z d_i\}}{Y_i}-\frac{1}{\theta^2}\sum_{i=1}^{n}(1/\theta+\delta_i+N_i)\frac{Z_{dij}\,T_i^{\alpha}\exp\{\beta Z_{di}\}}{Y_i^2}, \quad j=0,...,p_d; \quad (A.17)$$

$$\frac{\partial^2 LL}{\partial\theta\partial\gamma_j}=\frac{1}{\theta^2}\sum_{i=1}^{n}\frac{Z_{cij}T_i^{\phi}\exp\{\gamma Z_{ci}\}}{Y_i}-\frac{1}{\theta^2}\sum_{i=1}^{n}(1/\theta+\delta_i+N_i)\frac{Z_{cij}\,T_i^{\phi}\exp\{\gamma Z c_i\}}{Y_i^2}, \quad j=0,...,p_c; \quad (A.18)$$

$$\frac{\partial^2 LL}{\partial\beta_j\partial\beta_k}=-\sum_{i=1}^{n}(1/\theta+\delta_i+N_i)\frac{Z_{dij}Z_{dik}\,T_i^{\alpha}\exp\{\beta Z_{di}\}[1/\theta+T_i^{\phi}\exp\{\gamma Z_{ci}\}]}{Y_i^2}, \quad j,k=0,...,p_d; \quad (A.19)$$

$$\frac{\partial^2 LL}{\partial\beta_j\partial\gamma_k}=\sum_{i=1}^{n}(1/\theta+\delta_i+N_i)\frac{Z_{dij}Z_{cik}\,T_i^{\alpha}\exp\{\beta Z_{di}\}T_i^{\phi}\exp\{\gamma Z_{ci}\}}{Y_i^2}, \quad j=0,...,p_d,\ k=0,...,p_c;$$

$$(A.20)$$

$$\frac{\partial^2 LL}{\partial \gamma_j \partial \gamma_k} = - \sum_{i=1}^{n} (1/\theta + \delta_i + N_i) \frac{Z_{cij}Z_{cik} T_i^{\phi} \exp\{\gamma \mathbf{Z_{ci}}\}[1/\theta + T_i^{\alpha} \exp\{\beta \mathbf{Z_{di}}\}]}{Y_i^2}, \quad j,k = 0,\dots,p_c. \quad (A.21)$$

Figure 1
Conditional Survival Function
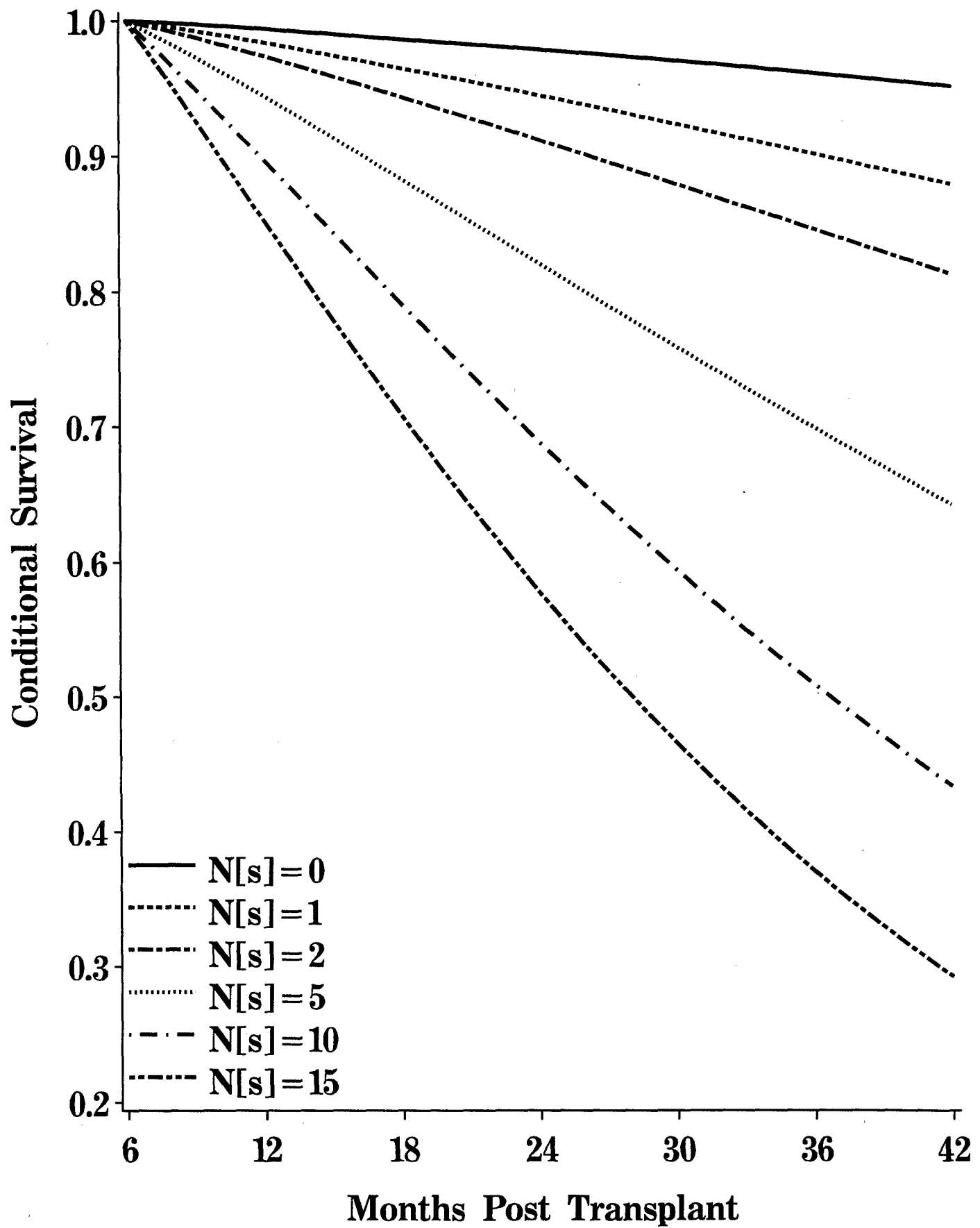
Figure 2

Conditional Survival Function Given 5 Transfusions at 6 Months
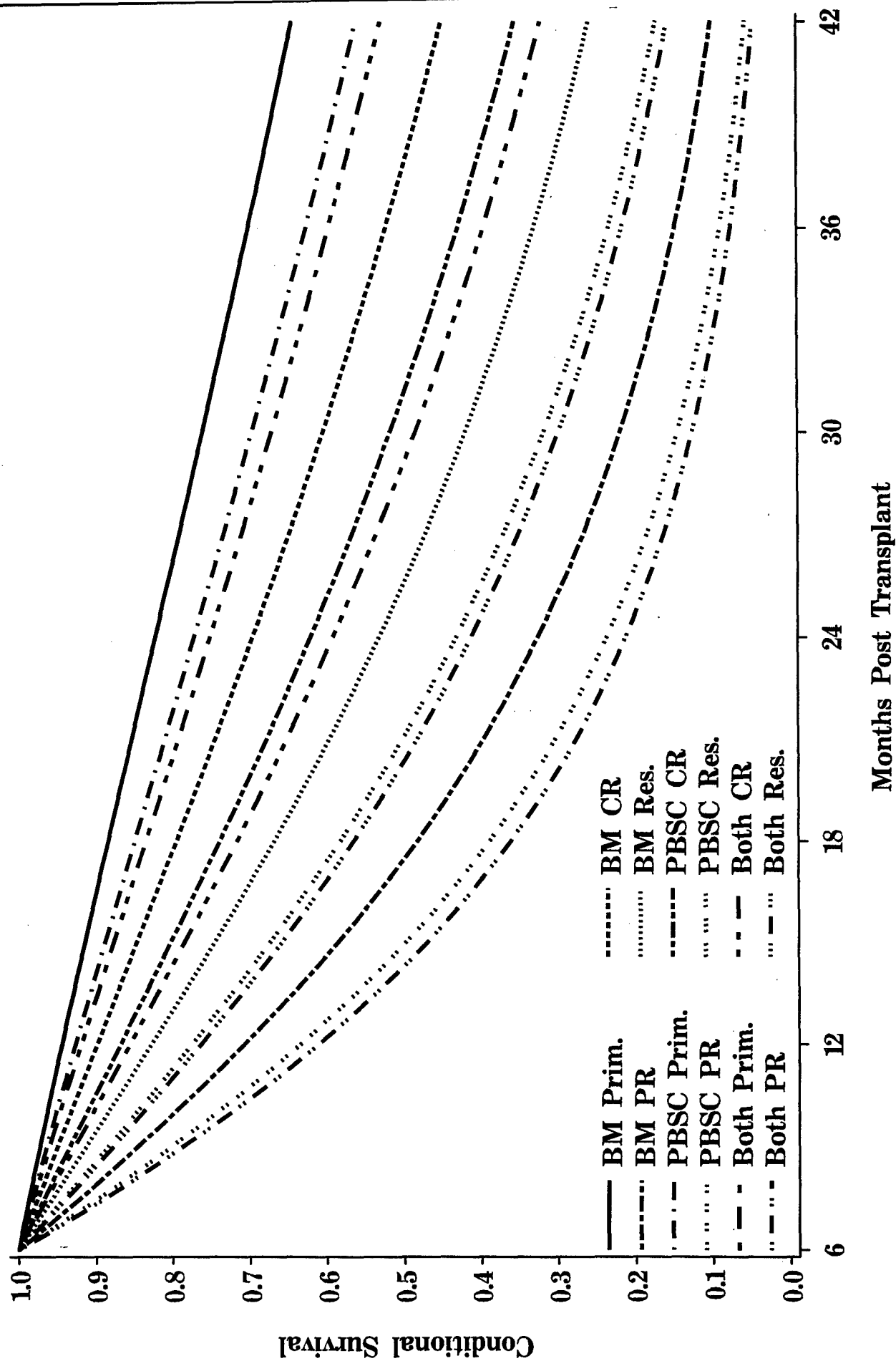
BM Prim.
BM PR
PBSC Prim.
PBSC PR
Both Prim.
Both PR

BM CR
BM Res.
PBSC CR
PBSC Res.
Both CR
Both Res.

Conditional Survival

Months Post Transplant

Testing For Center Effects In
Multicenter Survival Studies:
A Monte Carlo Comparison Of
Fixed And Random Effects Tests

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SUMMARY

The problem of testing for a center effect following a proportional hazards regression is considered. Two approaches to the problem can be used. One approach fits a proportional hazards model with a fixed covariate included for each center. The need for a center specific adjustment is evaluated using either a score, Wald or likelihood ratio test of the hypothesis that all the center specific covariates are equal to zero. An alternative approach is to introduce a random effect or frailty for each center into the model. Recently, Commenges and Andersen [1], have proposed a score test for this random effects model.

By a Monte Carlo study we compare the performance of these two approaches when either the fixed or random effects model holds true. The study shows that for moderate samples the fixed effects tests have nominal levels much higher than specified, but the random effect test performs as expected under the null hypothesis. Under the alternative hypothesis the random effect test has good power to detect relatively small fixed or random center effects. Also if the center effect is ignored the estimator of the main effect may be quite biased and the estimator is inconsistent. The tests are illustrated on a retrospective multicenter study of the recovery from bone marrow transplantation.

1. Introduction

A common question arising in multi-center prospective clinical trials and in retrospective studies from collaborative registry studies is whether some statistical adjustment is needed to account for effects specific to the individual centers contributing patients to the trial. Such an adjustment may be needed to account for factors, related to the outcome, which vary from center to center but are not adjusted for in the analysis. These factors may involve measurable quantities like a center's protocol for supportive therapy, the number of similar cases treated by the center, etc., or they be unmeasurable factors like the quality of the center's medical staff or differences in a center's catchment population.

In this paper we study two methods for testing the hypothesis of no center specific effect when the outcome measure is the time to some event. In such studies, typically, data is

analyzed using the Cox [2] proportional hazards regression model. The typical analysis includes covariates for the main effect of interest in the study as well as patient specific covariates which are related to the outcome of interest. The patient specific covariates are included in the final model in a partial attempt to make an adjustment for differences in patient demographics between institutions (See Klein and Moeschberger [3] for details on model building in this situation.)

The first method used to test for the presence of a center effect in such studies is the use of a fixed effect proportional hazards model. In this approach one institution is picked as a baseline institution and a set of indicator covariates are included for all other institutions. If we let Z denote the treatment and patient specific covariates and $X_i = \{1$ if the patient is from institution i; 0 otherwise$\}$, for $i = 1, \cdots, K$, where K is the number of institutions contributing to the study, then the hazard rate for the jth patient from institution i is

$$\lambda_{ij}(t|Z_{ij}) = \lambda_0(t) \exp\{\beta' Z_{ij} + \theta' X\} \tag{1}$$

where $X = (X_1, \cdots, X_{K-1})$. If there is no center specific effect in the study then $\theta_1 = \theta_2 = \cdots = \theta_{K-1} = 0$. To test the hypothesis of no center effect one can used a standard Wald, likelihood ratio or score test available in many statistical packages (See Andersen et al [4] or Klein and Moeschberger [3] for details).

An alternate approach to testing for a center effect is to use a random effects or frailty model. Such models were introduced by Clayton [5] and Vaupel et al. [6] and further discussed by, among others, Klein [7], Nielsen et al [8], Andersen et al. [4] and Klein and Moeschberger [3]. Here one assumes that the center specific effect for the ith center is represented by a mean 0, variance 1, unobservable random variable, ϵ_i, which acts multiplicatively on the hazard rate for all individuals within the center. That is

$$\begin{aligned}
\lambda_{ij}(t|Z_{ij}) &= \lambda_0(t) \exp\{\beta' Z_{ij} + \sigma \epsilon_i\} \\
&= \lambda_0(t) u_i \exp\{\beta' Z_{ij}\}
\end{aligned} \tag{2}$$

where $u_i = \exp\{\sigma \epsilon_i\}$. The ϵ_i's are an $i.i.d.$ sample from the unknown frailty distribution. In this model, the test of no center effect reduces to a test of the hypothesis that σ is equal to 0. Commenges and Andersen [1] have recently developed a score test of this hypothesis that does not require specification of the unknown frailty distribution. Computational details of this test are given in the Appendix.

In this paper we examine the relative performance of these two procedures by a Monte Carlo study. Details of the study are given in Section 2. In Section 3 we examine the performance of the two approaches when the null hypothesis is true. In Section 4 we examine the power of the two approaches when either the fixed or random effect model is true. In Section 5 we illustrate the use of the two statistics on a data set of allogeneic bone marrow transplants based on data from a collaborative bone marrow transplant registry. Finally, in Section 6 we summarize our conclusions and make some suggestions of how to proceed when the hypothesis of no center effect is rejected.

2. The Monte Carlo Study

To study the two approaches to testing for a potential center effect a Monte Carlo study was performed. In the study a single fixed time covariate, Z, was used. The covariate Z was taken to be $+1$ for half of the patients at each center and -1 for the remaining half. The value of the regression coefficient was taken to be either zero or $\ln(2)$. The baseline hazard rate was assumed to be one for all t. A random censoring time was generated for each subject from an exponential population with hazard rate equal to either $1/9$ or $3/7$. This leads to appoximately 10% or 30% of the observations being censored, respectively.

To investigate the relationship between the number of centers and the number of observations per center on the power of the tests we generated data coming from 5, 10 or 20 centers with a total of 100, 200, or 400 observations in the total sample. Data was generated from one of five models for the center effect. For the first case all observations were independent and no center effect was generated. This corresponds to the null case. For the other four cases data was generated either from a model with fixed center effects (1) or from the random effects model (2) with either a gamma, positive stable or inverse Gaussian frailty model. To make the model comparable for the random effects models the parameters of the frailty model were chosen to give a Kendall's τ of either 0.1, 0.3, or 0.5 between individuals within a center. Note since the inverse Gaussian model has a τ of less than 0.5 only the $\tau = 0.1$ and 0.3 cases were available.

For the gamma frailty model the u_i were simulated from a gamma distribution with mean 1 and variance α using the IMSL routine rngam. This model has a value of $\tau = \alpha/(\alpha + 1)$. For the inverse Gaussian distribution with probability density function $f(u) = (\eta\pi)^{-1/2} \exp\{2/\eta\} \exp\{-u/\eta - 1/(\eta u)\}$, the u_i were generated using the routine in Micheal et al [9]. For this model Kendall's τ is $0.5 - 2/\eta + (8/\eta^2) \exp\{4/\eta\} \int_{4/\eta}^{\infty} \exp(-u)/u\, du$. For the positive stable distribution with Laplace transform $\exp(-u^\rho)$, $0 \leq \rho \leq 1$, the u_i's were generated using results in Chambers et al [10]. Here Kendall's τ is $1 - \rho$. For the fixed center effects model we model the center effect as $\theta_i = c(i - 3)$, for $i = 1, \cdots, 5$ when $K = 5$ and as $\theta_i = c[-K - 2 + 2i]/2$, $i = 1, \cdots, K/2$ and $\theta_i = c[i - K/2]$ for $i = K/2, \cdots, K$ when $K = 10$ or $K = 20$. To determine the value of c we treat the θ_i as arrising from a discrete distribution, E, with mass $1/K$ at each θ_i. Then the expected value of E is zero as is the expected value of ϵ_i in (2). To find c we match the variance of $\exp\{E\}$ with that of the variance of the gamma frailty distribution. This gives a "association" in the fixed effects model of roughly the same strength as in the gamma frailty model. Note that while we treated the center effect in a random manner to get a value of c, in the simulation the values of c are fixed. Table 1 summarizes the parameters used in our study.

Table 1
Parameters used in The Monte Carlo Study

Center Effect		τ=0.1	$\tau = 0.3$	$\tau = 0.5$
Gamma		$\alpha = 2/9$	$\alpha = 6/7$	$\alpha = 2$
Positive Stable		$\rho = 0.9$	$\rho = 0.7$	$\rho = 0.5$
Inverse Gaussian		$\eta = 0.551$	$\eta = 4.070$	Not Possible
Constant	K=5	c=0.311	c=0.534	c=0.709
	K=10	c=0.132	c=0.230	c=0.305
	K=20	c=0.007	c=0.122	c=0.161

For each sample we compute the Wald, likelihood ratio and score test for the fixed effects model, the score test for the random effects model and the estimate of the β based on a proportional hazards model which does not adjust for center effects and for the model which makes a fixed effect adjustment for the center effects. This is done in each run for 5,000 samples. We estimate the power of the four test of center effects at a 0.05 significance level and the bias and mean squared error of the two estimates of β.

3. Signficance levels of the tests

Table 2 shows the estimated null power of the likelihood ratio fixed effects test and the random effects score test, at a 0.05 significance level, based on 5,000 replicates for each combination of β, K and total sample size. Here we have reported only the likelihood ratio test for the fixed effects model since its performance was in all cases the best of the three possible fixed effects test statistics. From this table we first see that the test based on a fixed center effects model requires a very large sample size before it achieves the desired level. When the number of subjects at each center is small the test is anti-conservative. This fact appears to be true even when there are ten or more groups with 400 total observations and the results suggest that unless the number of subjects in each group is very large the fixed effect test should not be used because it rejects the hypothesis of no center effect too often when the null hypothesis is true.

For the random effects score test, with only a few exceptions, the nominal level of the test is achieved. When $K = 5$ and the total sample is 100 the test may be slightly anti-conservative, but the estimated power achieved is closer to 0.05 than for any of the fixed effects tests.

4. Behavior When There Is A Group Effect

As seen in the previous section the fixed effects test for a group effect tends to reject the null hypothesis of no group effect too often when the number of subjects per group is small. The random effects test does, however, appear to maintain the correct significance level for these small sample cases. In our examination of the power of these tests we found that the power of the fixed effects test was higher in all cases than the random effects test. However,

due to the problem with the fixed effects test when the null hypothesis is true these higher powers give a false impression that this test is performing better than the random effects test. Higher power is to be expected since the nominal significance levels of the fixed effects tests are higher than those of the random effects test.

To examine the power of the random effects tests we report in Table 3 the estimated power of the random effects tests for $\tau = 0.1$ and 0.3 for the gamma, inverse Gaussian, and positive stable frailty models and the fixed effects models. When $\tau = 0.5$ for the gamma, positive stable random effects models and for the fixed effects model, all tests essentially have a power of 1. From this table we see that the random effects test has good power to detect fixed group effects. The power is quite high for all types of group effects for small associations between individuals within a group when the total sample size is large or the number per group is large. For a given number of groups and a given total sample size the power decreases as the censoring fraction increases.

While the random effects test for group effects has reasonable power to detect these effects a natural question is whether the presence of a group effect has an effect on the estimate of treatment efficacy. To examine this question we studied the relative excess bias in estimating β in a model that ignores the center effect when such an effect exists. We computed for each combination of the total sample size N, number of groups K, the degree of association, τ, and group effect β the quantity

$$r = \frac{B(0) - B(\tau)}{|B(0)|}, \tag{3}$$

where $B(\tau)$ is the estimator of the bias of the estimator of β based on a model which ignores the center effect. Here $B(0)$ is from data simulated from a model with no center effect.

We analysed these data using ANOVA techniques as in Andersen et al. [11]. Separate analyses were made for $\beta = 0$ and $\beta = \ln(2)$ and we included the factors $N * K$, τ, percent CENSoring, and DISTribution of the center effects since inclusion of more interactions did not improve the fit of the model. That is, the model used for both values of β was

$$E(r) = \alpha + \beta_{N*K} + \gamma_\tau + \delta_{\text{CENS}} + \varepsilon_{\text{DIST}}.$$

For $\beta = 0$ none of these factors had any significant effect on r which, as one would expect, was small in all cases. For $\beta = \ln(2)$, $E(r)$ was everywhere larger than for $\beta = 0$. That is because under the random effects models and apparantly under the constant effects models as well the estimates computed without adjustment for center effects tend to shrink towards zero. Furthermore, $E(r)$ increased in absolute value as the strength of association, τ, increases. Thus the averages over the other factors in the model were -17.2, -45.2, and -70.9 for $\tau = 0.1$, 0.3, and 0.5, respectively. The amount of censoring had no effect and the type of distribution and the number of groups, K, had little effect on r whereas $E(r)$ increased in absolute value when the total sample size, N, increases, the averages over the other factors in the model being -19.3, -41.7, and -72.7 for $N = 100$, 200 and 400, respectively.

This suggests that the estimators computed by ignoring either a fixed or random effect are inconsistent. It implies that the so called marginal approach of Lee et al [12] or Wei et al [13] which computes the estimate of β under an independent working model and uses a robust variance estimator is not appropriate in this problem.

5. Example

To illustrate the tests we consider a sample of 609 Acute Myelogenous Leukemia (AML) patients reported to the International Bone Marrow Transplant registry (IBMTR). All patients were given an HLA-identical sibling transplant for the leukemia which was in their first complete remission at the time of transplant. The IBMTR is an international cooperative group which collects data on allogenic transplants conducted world wide. The sample here consists of data reported by the 60 largest reporting centers over the period 1988-1994. Each center contributed at least 5 transplants to the study and had at least one patient relapsing or dying. Table 4 shows the distribution of the number of cases per center.

The goal of the study was to model the relationship between the patient's age (dichotomized as ≤ 30 versus >30) and Karnofski score (<90 versus ≥ 90) at the time of transplant and treatment failure. The treatment is said to fail if the patient dies or relapses. Ignoring any possible center effects the estimates of the risk coefficients were 0.26 (se=0.13, p=0.05) for the effect of being over thirty at transplant and 0.32 (se=0.17, p=0.07) for having a Karnofski score under 90. The four tests for a possible group effect give the following results:

Fixed Effects	
Likelihood ratio Test	p=0.228
Score Test	p=0.008
Wald Test	p=0.104
Random Effects	p=0.996

Note that the fixed effects score test suggests the presence of a center effect while the other tests do not show evidence of a center effect. In light of our simulation results which show that the score test rejects too often we conclude that their is no need here to adjust for a center effect. Note that if we had chosen to adjusts for a fixed center effect then the estimates for the risk coefficients would be 0.33 (se=0.15, p=0.024) for age and 0.25 (se=0.22, p=0.249) for Karnofski score which would lead to somewhat different conclusions than the model without a group effect.

6. Discussion

Our Monte Carlo study has shown that the use of a fixed effects model to test for a center effect in a small to moderate size multi-center trial tells us too often that an adjustment for such an effect is needed when in fact there is no such effect. This test requires a large number

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of subjects in each center to give significance levels close to the nominal level. The sample sizes needed in each center are much larger than what is commonly encountered in practice. The random effects test of Commenges and Andersen [1] seems to behave quite well under the null hypothesis of center effect even when the number of observations in each group is fairly small and it seems to have reasonable power to detect either a fixed or random group effect.

The random effects test has a few additional advantages over the fixed effects test. First, the estimates of the center effect in the fixed effects proportional regression model requires at least one event for each center. When this does not hold the estimates do not exist. This restriction is not required for the random effects model. Second, when all the events in one center occur before (or after) all the events at an other center then the estimates of that center's fixed effect is at minus infinity (or plus infinity). Again this is not a problem for the random effects test. Finally, the Wald and likelihood ratio tests for fixed effects test requires the maximization of a log likelihood which is a function of $p + (K - 1)$ parameters, where p is the number of patient specific covariates. When there is a large number of centers this may be a large number of parameters and numerical problems may occur if good starting values are not used. Note that the random effects test requires maximization with respect to only p covariates.

When the presence of a center effect is detected then the natural question arrises as to how adjust for this effect. As noted earlier some adjustment is needed since the presence of a center effect, either fixed or random, makes the estimators of the risk coefficients computed under an assumption of no center effect inconsistent. The suggestion of Liang et al. [14] to use an independence working model in this case and a robust estimator of the variance of the estimator is not appropriate since the estimators do not seem to be consistent in these cases.

Some model which incorporates the center effect is needed. One possibility is to use the fixed effects model for this adjustment. This model can be fit using standard statistical software. We looked at the relative excess bias (3) of this main effect adjusted for a fixed center effect as compared to the bias under the independence model (data not shown) and in this case, as opposed to the unadjusted relative bias studied above, the relative bias decreased as the sample size increases. This was true, not only when the fixed effects model is correct, but is also true when the random effect model is true. This suggests that this model may provide a quick means of making a crude adjustment for a center effect when the sample sizes are large. A second possibility would be to estimate the treatment effect in a Cox regression model *stratified* by center but then centers with no events would contribute no information to the estimate.

An alternative to using fixed effect models to adjust for a center effect would be to use a frailty model. The technology for fitting a proportional hazards model with a fixed effect can be found in Nielsen et al [8], Klein [6] and Andersen et al [15], for the gamma frailty model and Klein et al [16] for the inverse Gaussian model and Wang et al [17] for the positive stable model.

Acknowledgements

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Table 2. Estimated Null Power Of The Fixed and Random Effects Tests

Total Sample Size	Number of Groups	Percent Deaths	β	Likelihood Ratio	Random Effects Test
100	5	0.7	0.00	0.0674**	0.0588*
100	5	0.7	0.69	0.0540	0.0538
100	5	0.9	0.00	0.0670**	0.0626**
100	5	0.9	0.69	0.0590*	0.0582*
100	10	0.7	0.00	0.0802**	0.0610**
100	10	0.7	0.69	0.0774**	0.0532
100	10	0.9	0.00	0.0860**	0.0592*
100	10	0.9	0.69	0.0816**	0.0498
100	20	0.7	0.00	0.1592**	0.0590*
100	20	0.7	0.69	0.1486**	0.0526
100	20	0.9	0.00	0.1996**	0.0556
100	20	0.9	0.69	0.1494**	0.0552
200	5	0.7	0.00	0.0590*	0.0608**
200	5	0.7	0.69	0.0566*	0.0564*
200	5	0.9	0.00	0.0640**	0.0556
200	5	0.9	0.69	0.0520	0.0530
200	10	0.7	0.00	0.0704**	0.0572*
200	10	0.7	0.69	0.0600**	0.0568*
200	10	0.9	0.00	0.0690**	0.0508
200	10	0.9	0.69	0.0652**	0.0564*
200	20	0.7	0.00	0.0948**	0.0556
200	20	0.7	0.69	0.0956**	0.0544
200	20	0.9	0.00	0.1032**	0.0578*
200	20	0.9	0.69	0.0926**	0.0508
400	5	0.7	0.00	0.0550	0.0528
400	5	0.7	0.69	0.0508	0.0566*
400	5	0.9	0.00	0.0564*	0.0566*
400	5	0.9	0.69	0.0556	0.0626**
400	10	0.7	0.00	0.0542	0.0556
400	10	0.7	0.69	0.0604**	0.0580*
400	10	0.9	0.00	0.0584*	0.0490
400	10	0.9	0.69	0.0562*	0.0500
400	20	0.7	0.00	0.0670**	0.0462
400	20	0.7	0.69	0.0690**	0.0534
400	20	0.9	0.00	0.0736**	0.0506
400	20	0.9	0.69	0.0668**	0.0470

**-more than 3 SE larger than the nominal level
*- 2-3 SE larger than the nominal level.

Table 3. Power Of The Random Effects Test For Group Effects

N	K	β	τ	Constant		Gamma		Inverse Gaussian		Positive Stable	
				70% Dead	90% Dead	70% Dead	90% Dead	70% Dead	90% Dead	70% Dead	90% Dead
100	5	0.00	0.1	0.659	0.784	0.538	0.618	0.555	0.644	0.446	0.486
100	5	0.00	0.3	0.995	1.000	0.909	0.942	0.903	0.952	0.891	0.921
100	5	0.69	0.1	0.638	0.767	0.541	0.620	0.542	0.630	0.444	0.477
100	5	0.69	0.3	0.994	1.000	0.903	0.944	0.902	0.953	0.890	0.911
100	10	0.00	0.1	0.495	0.619	0.502	0.619	0.485	0.608	0.454	0.466
100	10	0.00	0.3	0.979	0.996	0.944	0.984	0.948	0.986	0.947	0.963
100	10	0.69	0.1	0.470	0.612	0.495	0.608	0.481	0.598	0.440	0.454
100	10	0.69	0.3	0.972	0.996	0.939	0.979	0.944	0.983	0.943	0.964
100	20	0.00	0.1	0.278	0.386	0.301	0.501	0.297	0.451	0.289	0.303
100	20	0.00	0.3	0.850	0.937	0.839	0.978	0.871	0.977	0.923	0.948
100	20	0.69	0.1	0.271	0.381	0.313	0.492	0.299	0.431	0.272	0.278
100	20	0.69	0.3	0.841	0.938	0.861	0.980	0.881	0.978	0.924	0.942
200	5	0.00	0.1	0.967	0.994	0.784	0.846	0.790	0.853	0.624	0.680
200	5	0.00	0.3	1.000	1.000	0.975	0.986	0.969	0.986	0.960	0.977
200	5	0.69	0.1	0.954	0.987	0.777	0.842	0.778	0.845	0.610	0.661
200	5	0.69	0.3	1.000	1.000	0.971	0.979	0.971	0.987	0.955	0.974
200	10	0.00	0.1	0.902	0.973	0.827	0.894	0.824	0.901	0.689	0.730
200	10	0.00	0.3	1.000	1.000	0.996	0.999	0.995	0.999	0.990	0.997
200	10	0.69	0.1	0.897	0.964	0.814	0.886	0.826	0.895	0.672	0.717
200	10	0.69	0.3	1.000	1.000	0.995	0.998	0.997	0.999	0.991	0.995
200	20	0.00	0.1	0.767	0.875	0.767	0.877	0.776	0.876	0.659	0.696
200	20	0.00	0.3	1.000	1.000	0.997	1.000	0.999	1.000	0.998	0.999
200	20	0.69	0.1	0.741	0.866	0.757	0.871	0.746	0.867	0.651	0.671
200	20	0.69	0.3	1.000	1.000	0.998	1.000	0.998	1.000	0.997	1.000
400	5	0.00	0.1	1.000	1.000	0.920	0.942	0.927	0.952	0.766	0.814
400	5	0.00	0.3	1.000	1.000	0.993	0.996	0.992	0.995	0.987	0.993
400	5	0.69	0.1	1.000	1.000	0.924	0.947	0.920	0.949	0.765	0.809
400	5	0.69	0.3	1.000	1.000	0.993	0.997	0.991	0.996	0.985	0.993
400	10	0.00	0.1	0.999	1.000	0.974	0.990	0.974	0.990	0.861	0.891
400	10	0.00	0.3	1.000	1.000	1.000	1.000	1.000	1.000	0.999	1.000
400	10	0.69	0.1	0.999	1.000	0.964	0.983	0.972	0.988	0.854	0.895
400	10	0.69	0.3	1.000	1.000	1.000	1.000	1.000	1.000	0.999	1.000
400	20	0.00	0.1	0.995	1.000	0.983	0.992	0.983	0.994	0.900	0.924
400	20	0.00	0.3	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
400	20	0.69	0.1	0.993	0.999	0.979	0.992	0.979	0.993	0.895	0.921
400	20	0.69	0.3	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Table 4. The Distribution Of The Number Of Cases Per Center

Number Of Cases	Number Of Centers
5	11
6	13
7	7
8	6
10	2
11	5
12	2
13	1
14	1
15	2
17	1
18	1
19	2
20	2
22	1
26	1
28	1
34	1

Appendix

For the *jth* subject $j = 1, \ldots, S_i$ in the *ith* group $i = 1, \ldots, n$ let T_{ij} be the observation time of subject and $D_{ij} = 1$ if subject died and 0 otherwise. The frailty model (2) proposed in Section 1 can be specified as a counting process $N_{ij} = I(T_{ij} \leq t, D_{ij} = 1)$ with

$$dN_{ij}(s) = dM_{ij}(s) + Y_{ij}(s) \exp\{\sigma \varepsilon_i + \beta' z_{ij}\} \lambda_0(s) \, ds,$$

where $Y_{ij}(s) = I(T_{ij} > s)$, $M_{ij}(\cdot)$ is a martingale, ε_i's are *iid* random variables with an unspecified distribution G which has mean 0 and variance 1.

Let $\bar{N} = \sum_{i,j} N_{ij}$, $S^{(0)}(\beta, s) = \sum_{i,j} Y_{ij}(s) \exp(\beta' z_{ij})$, and $\widehat{\beta}$ be the maximum partial likelihood estimate of β under the null hypothesis of $\sigma = 0$. The cumulative baseline hazard function $\Lambda_0(t) = \int_0^t \lambda_0(s) ds$ can be estimated by

$$\widehat{\Lambda}_0(t) = \int_0^t \frac{d\bar{N}(s)}{S^{(0)}(\widehat{\beta}, s)}.$$

Then the martingale $M_{ij}(t)$ can be estimated as

$$\widehat{M}_{ij}(t) = N_{ij}(t) - \widehat{\Lambda}_{ij}(\widehat{\beta}, t),$$

where $\widehat{\Lambda}_{ij}(\beta, t) = \exp(\beta' z_{ij}) \widehat{\Lambda}_0(t)$.

Let $p_{ij}(\beta, s) = Y_{ij}(s) \exp(\beta' z_{ij}) / S^{(0)}(\beta, s)$ and $p_i(\beta, s) = \sum_j p_{ij}(\beta, s)$. To test the hypothesis of homogeneity of $\sigma = 0$, the score test statistic is given by

$$T(\widehat{\beta}) = \sum_{i=1}^n \left(\sum_{j=1}^{S_i} \widehat{M}_{ij}(t) \right)^2 - \bar{N}(\infty) + \int_0^\infty \sum_{i=1}^n p_i^2(\widehat{\beta}, s) d\bar{N}(s).$$

Let $H_i(\beta, s) = 2 \left\{ \widehat{M}_i(s) - \sum_{l=1}^n \widehat{M}_l(s-) p_l(\beta, s) - p_i(\beta, s) + \sum_{l=1}^n p_l^2(\beta, s) \right\}$, where $\widehat{M}_i(s) = \sum_j \widehat{M}_{ij}(s)$. The variance of $T(\widehat{\beta})$ can be consistently estimated by

$$\widehat{I}_c = \widehat{I}(\widehat{\beta}) - \widehat{J}(\widehat{\beta}) I_{\widehat{\beta}}^{-1} \widehat{J}(\widehat{\beta})',$$

where $I_{\widehat{\beta}}^{-1}$ is the information matrix relative to $\widehat{\beta}$,

$$\widehat{I}(\beta) = \sum_{i=1}^n \int_0^\infty H_i^2(\beta, s) \, p_i(\beta, s) \, d\bar{N}(s), \text{ and}$$

$$\widehat{J}(\beta) = \sum_{i=1}^n \int_0^\infty H_i(\beta, s) \sum_{j=1}^{S_i} z_{ij} \, p_{ij}(\beta, s) \, d\bar{N}(s).$$

Then the test statistic for homogeneity is $H = T(\widehat{\beta}) / \sqrt{\widehat{I}_c}$ which has an asymptotic standard normal distribution under the null hypothesis.

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MODELING COVARIATE ADJUSTED MORTALITY RELATIVE TO A STANDARD POPULATION: DOES BONE MARROW TRANSPLANTATION PROVIDE A CURE?

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SUMMARY

A study of long term survival of 1,487 patients given an allogenic bone marrow transplant for acute myelogenous leukemia and 729 patients given a transplant for severe aplastic anemia was conducted by the International Bone Marrow Transplant registry. One aim of this study is to determine if the mortality rates of these patients returns after some period of time to the same mortality rate as in the general population. To examine this question a model for the relative mortality of a bone marrow transplant patient relative to a matched individual in the general population is presented. This model allows for different relative mortality rates depending on the risk factors the patient may have. We discuss an estimation procedure for this model and construct a test that the mortality rate in the transplanted population is the same as in the reference population over a given time interval.

1 Introduction

Allogenic bone marrow transplantation has been a common treatment for leukemia, aplastic anemia and genetic disorders. In the past twenty years the number of patients treated by means of this therapy has greatly increased[1] so that now this is a standard treatment for patients with acute myelogenous leukemia (AML)[2] and severe aplastic anemia (SAA)[3]. While the short term effects of this treatment modality have been studied extensively, with few exceptions[4] there has been little study of the long term effects on patient survival.

Numerous studies have been conducted to determine risk factors for bone marrow transplants. These studies have focused on making comparisons between bone marrow transplantation patients or on comparisons of the effectiveness of transplantation therapy to

chemotherapy. These studies, based on a Cox regression model[5], provide relative risk estimates of treatment modalities or prognostic indications. All estimates are relative to other patients with the disease.

With increasing follow-up of transplant patients it is natural to ask if bone marrow transplant in fact "cures" all patients or some subgroup of patients. Here, by "cured" we mean the patient's mortality rate has returned to the same mortality rate as one would expect in a person of the same age and gender in the general population. While it is not reasonable to expect a return to the standard mortality rate of the general population immediately after transplant, it is possible that after some time the excess mortality directly related to the therapy may have washed out. Of interest is the estimation of this time of "cure" or the testing at a fixed time point to determine if the patient has been cured. It is also highly likely that this cure time may depend on some risk factors either known at the time of transplantation or by some point in time in the patients post transplant recovery process.

Twenty-five years ago the International Bone Marrow Transplant Registry (IBMTR) was found with the goal of collecting data on consecutive allogeneic marrow transplants from member centers[6]. The IBMTR is a volunteer organization of 406 transplant teams worldwide that report all their consecutive cases to a central statistical center. Approximately 40% of the allogeneic transplants performed are reported to the Registry. Extensive data on patient risk factors is collected at the time of transplantation on most patients and patient follow-up information is obtained every six months.

In this note we shall present a model for the excess relative mortality due to transplantation in a group of 1,487 AML and 729 SAA patients from 14 countries. All patients included in the sample were alive and free of their primary disease at two years post transplant, so that all deaths observed in the sample are from causes not related to the short term toxicity of the transplant itself. All patients were transplanted between 1980 and 1993. This is a subsample of a larger sample previously reported[4] on which we were able to obtain current published life table information. Table 1 shows the distribution of the number of cases by the country where the patient was transplanted. Standard mortality tables were obtained for these countries by sex and for the US by sex and race (black versus non-black).

Of the 1,487 AML patients 160 died, while 34 of the 729 SAA patients died. For the AML patients the median follow-up was 6.2 years with a range of 2-16.7 years. For the aplastic anemia patients the median follow-up time was 6.7 years with a range of 2-16.8 years. The median age of the AML patients at the time of transplantation was 22.4 years (range 0.5-56.6 years) and was 18.8 years (range 0.2-69.4 years) for SAA patients.

There are a number of factors that have been shown to be predictive of survival following a transplant. One important factor is the development of graft-versus-host disease (GVHD). Two types of GVHD can occur, acute GVHD which occurs in the first 100 days post transplant and chronic GVHD which occurs after 100 days. We include as risk factors for survival a binary indicator of whether the patient had acute GVHD, an indicator of whether a patient had chronic GVHD prior to two years that was still active at two years, and indicator of whether a patient had chronic GVHD prior to two years that was resolved at two years. Age of the patient at the time of transplantation has been found to be associated with survival

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in transplant studies using the Cox model. While we shall be making an adjustment for age by using the age specific survival rates from published life tables, it is still of interest to see if young patients have a different "cure" rate then older patients. We divided the patients into three age groups: children (age$\leq$16 years), young patients (16-25 years) and older patients (> 25 years). A final covariate to be considered is the stage of the disease at the time of transplantation. For AML patients we classify patients as having early (transplanted in first complete remission), intermediate (transplanted in a second or later complete remission) or advanced (transplanted in relapse) disease. For SAA patients patients are classified as having earlier disease (time from diagnosis to transplant less than one year) or advanced disease (time from diagnosis to transplant more than one year). Table 2 summarizes the covariates for the two diseases.

To examine the effects of these covariates on survival the standard Cox regression model was fit to the data. For this model the hazard rate of an individual with covariate vector Z is of the form

$$h(t|Z) = h_0(t) \exp\{\gamma^t Z\}, \tag{1.1}$$

where γ is the vector of covariates and $h_0(t)$ is a baseline hazard rate. Here the risk coefficients, γ, provide information on the relative effects of the covariates on survival among transplant patients and $h_0(t)$ is the death rate for, in our example, a child transplant patient with early disease who has had neither type of GVHD. The results of fitting the standard Cox model are given in Table 3. These results show that for AML transplant patients, those with active chronic GVHD and intermediate or advanced disease tend to have lower survival, relative to other AML transplant patients. For SAA patients those with either acute GVHD or active chronic GVHD and advanced disease, tend to have lower survival, relative to other SAA transplant patients.

In the next section we present a model for the survival of bone marrow transplant patients relative to the survival rates in the general population. The estimated relative mortality is allowed to be effected by a patient's risk factors at the time of transplant. We develop a test of the hypothesis that the relative mortality is equal to one over a given time interval. This is a test that the mortality rate in the treated population over this interval is the same as that in the general population. In Section 3 we return to the example to determine at various times after transplant if a patient with a certain set of covariates has a mortality rate which has returned to normal.

2   A Model for Excess Relative Mortality

For each patient we assume that the mortality rate of a patient of the same age and sex (and possibly race) is known. At a time, t, after transplant let $\mu_i(t)$ be the standard mortality rate of the patient in the general population. Note that if the patient were transplanted at age a, then $\mu_i(u)$ is the mortality rate in the general population of a patient of age $a + u$. For the ith patient we have covariates $Z_i = (Z_{i1}, \cdots, Z_{ip})^t$.

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The death rate of the ith patient at t years post transplant is modeled as:

$$\lambda_i(t|\boldsymbol{Z}_i) = \alpha_0(t)\mu_i(t)\exp\{\boldsymbol{\beta}^t\boldsymbol{Z}_i\}, \tag{2.2}$$

where $\alpha_0(t)$ is a baseline relative mortality due to transplantation and $\boldsymbol{\beta}^t = (\beta_1, \cdots, \beta_p)$ is a p-vector of covariate to be estimated from the data. Note that this model is of the form of the usual proportional hazards regression model with the inclusion of a time dependent covariate, $\ln[\mu_i(t)]$ with a regression parameter constrained to be one.

Model (2.2) was orginally proposed by Andersen et al[7] as a model for relative mortality. When $\alpha_0(t)$ is fixed at one this is the model of Breslow et al[8]. When there are no covariates this is the model of Andersen and Væth[9].

To estimate parameters of the model, let T_i be the on study time and δ_i be the death indicator ($\delta_i = 1$ if T_i is a death, 0 otherwise) for the ith patient. Define the counting process $N_i(t) = I\{T_i \leq t, \delta_i = 1\}$ and $Y_i(t) = I\{T_i \geq t\}$, where $I\{\cdot\}$ is the indicator function. Let $\bar{N}(t) = \sum_i N_i(u)$, $S_0(t, \boldsymbol{\beta}) = \sum_i Y_i(t)\mu_i(t)\exp\{\boldsymbol{\beta}^t\boldsymbol{Z}_i\}$. Define the p-vector $\boldsymbol{S}_1(t, \boldsymbol{\beta}) = \sum_i \boldsymbol{Z}_i Y_i(t)\mu_i(t)\exp\{\boldsymbol{\beta}^t\boldsymbol{Z}_i\}$ and the $p \times p$ matrix $\boldsymbol{S}_2(t, \boldsymbol{\beta}) = \sum_i \boldsymbol{Z}_i\boldsymbol{Z}_i^t Y_i(t)\mu_i(t)\exp\{\boldsymbol{\beta}^t\boldsymbol{Z}_i\}$. Using standard counting process techniques[10] the log partial likelihood is

$$L(\boldsymbol{\beta}) = \sum_i \int_0^T \boldsymbol{\beta}^t\boldsymbol{Z}_i dN_i(u) - \int_0^T \ln\{S_0(u, \boldsymbol{\beta})\}d\bar{N}_i(u), \tag{2.3}$$

where T is the maximum on study time. The maximum partial likelihood estimators of $\boldsymbol{\beta}$ are found by solving the score equations

$$\boldsymbol{U}(\boldsymbol{\beta}, T) = \sum_i \int_0^T dN_i(u) - \int_0^T \frac{\boldsymbol{S}_1(u, \boldsymbol{\beta})}{S_0(u, \boldsymbol{\beta})}d\bar{N}(u) = 0, \tag{2.4}$$

and information matrix is given by

$$\boldsymbol{I}(\boldsymbol{\beta}, T) = \int_0^T \left\{ \frac{\boldsymbol{S}_2(u, \boldsymbol{\beta})}{S_0(u, \boldsymbol{\beta})} - \left[\frac{\boldsymbol{S}_1(u, \boldsymbol{\beta})}{S_0(u, \boldsymbol{\beta})} \right]^2 \right\} d\bar{N}(u). \tag{2.5}$$

The estimated covariance matrix of the $\hat{\boldsymbol{\beta}}$'s is given by $\hat{\boldsymbol{\Sigma}} = \boldsymbol{I}(\hat{\boldsymbol{\beta}}, T)^{-1}$.

The cumulative relative mortality due to transplantation, for an individual with a covariate vector $\boldsymbol{Z}_0$, over the interval $[s, t]$ is given by

$$A(s, t, \boldsymbol{Z}_0) = A_0(s, t)\exp\{\boldsymbol{\beta}^t\boldsymbol{Z}_0\}, \tag{2.6}$$

where

$$A_0(s, t) = \int_s^t \alpha_0(u)du. \tag{2.7}$$

The quantity $A_0(s, t)$ can be estimated consistently by

$$\hat{A}_0(s, t) = \int_s^t \frac{d\bar{N}(u)}{S_0(u, \hat{\boldsymbol{\beta}})}. \tag{2.8}$$

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Applying Andersen et al[10] Corollary VII.2.6. with $Y_i(t)$ replaced by $Y_i(t)\mu_i(t)$, it can be shown that a consistent estimator for the variance of $\hat{A}(s,t,\boldsymbol{Z}_0) = \hat{A}_0(s,t)\exp\{\hat{\beta}_t\boldsymbol{Z}_0\}$ is given by

$$Var\left[\hat{A}(s,t,\boldsymbol{Z}_0)\right] = \left[\exp\{\hat{\beta}^t\boldsymbol{Z}_0\}\right]^2\left\{\int_s^t \frac{d\bar{N}(u)}{S_0(u,\hat{\beta})^2} + \hat{\boldsymbol{W}}^t\hat{\Sigma}\hat{\boldsymbol{W}}\right\}, \qquad (2.9)$$

where

$$\hat{\boldsymbol{W}} = \int_s^t \left\{\frac{S_1(u,\hat{\beta})}{S_0(u,\hat{\beta})} - \boldsymbol{Z}_0\right\}\frac{d\bar{N}(u)}{S_0(u,\hat{\beta})}. \qquad (2.10)$$

Using $\hat{A}(s,t,\boldsymbol{Z}_0)$ and $Var[\hat{A}(s,t,\boldsymbol{Z}_0)]$ we may test the hypothesis that the mortality rate for an individual with a set of covariates, $\boldsymbol{Z}_0$, is the same as in the general population over the interval $[s,t]$. If the mortality rates are equal over the interval then $\alpha_0(u)e^{\beta^t\boldsymbol{Z}_0} = 1$, for all $u \in [s,t]$ and $A(s,t,\boldsymbol{Z}_0) = (t-s)$. The test statistic is given by

$$Q(s,t) = \frac{\hat{A}(s,t,\boldsymbol{Z}_0) - (t-s)}{Var[\hat{A}(s,t,\boldsymbol{Z}_0)]^{1/2}} \qquad (2.11)$$

which has a large sample standard normal distribution when the null hypothesis is true. Large positive values of $Q(s,t)$ favor the alternative hypothesis (since relative rates lower than one are not biologically feasible) so that the null hypotheses is rejected when $Q(s,t)$ is larger than the appropriate upper percentile of a standard normal.

3   Estimates of Relative Mortality for BMT Patients

To apply the inference procedure discussed in the previous Section to BMT patients with AML or SAA we first need to obtain the population mortality rates, $\mu_i(\cdot)$, for each patient. To obtain these rates we asked IBMTR team members in each of the countries listed in Table 1 to provide us with population mortality data. For all countries, except the United Kingdom, this information came to us in the form of a life table. For the UK population death rates, by sex, for the year 1991 were obtained directly from the Office of Population Census and Surveys. Unabridged life table estimates of the population survival probabilities by sex were obtained from government sources for the 1992 Australian, 1988 Brazilian, 1985-7 Canadian, 1986-1990 Danish, 1992 Japanese, 1985-6 Spanish, 1991 Swedish and 1989 American (by race) survival. These provide the values of the population survival rate, $S(x)$, for ages $x = 0,1,2,\cdots$. For the Netherlands, based on the 1980-4 life table, estimates of $S(x)$ were available at ages $0.5, 1.5, 2.5, \cdots$ years. Estimates for other countries were from abridged tables. For the 1986-7 German (FRG) life table, estimates of $S(x)$ were available for $x = 0,1,2,5,10,\cdots$. For Italy (1985 table) and Portugal (1991 tables), estimates were available at $x = 0,1,5,10,\cdots$.

From these tables we compute the population mortality rate, $\lambda(a)$, at age a by assuming a constant mortality over the interval reported in the population life table. Under this assumption for an unabridged life table we have

$$\lambda(a) = -\ln[S(x+1)] - (-\ln[S(x)]), \quad \text{for} \quad x \leq a < x+1,$$

while for a table with five year intervals we compute

$$\lambda(a) = -\ln[S(x+5)] - (-\ln[S(x)])/5, \quad \text{for} \quad x \leq a < x+1.$$

Once the population mortality rates are computed the value of $\mu_i(t)$ for a patient of age a_i at transplant is given by $\lambda(a_i + t)$, where $\lambda(\cdot)$ is from the proper age (race) and sex matched population. Using these population rates we obtain the estimates of the relative mortality risk coefficients by maximizing (2.3). The estimates are given in Table 4.

An examination of Table 4 shows that there is a significant effect of age on the relative mortality rate. Patients who are younger are dying at a faster rate than older patients relative to the age matched mortality rates in the general population. Note that in the standard Cox model (Table 2), where comparisons are between transplanted patients, there is no age effect for either disease. If there is no effect of age on transplant outcomes then the finding of an age effect in the relative mortality model is not surprising since younger patients have a lower population mortality rate. For both diseases the estimates of the effects of the other covariates are similar in the Cox model and the relative mortality model.

In Figures 1 and 2 we plot a smoothed estimate of the relative mortality rate, $\hat{\lambda}_0(t) \exp(\hat{\beta} Z_0)$ for an AML and SAA patient in each of the three age groups. The plots are for patients who had not had graft-versus-host disease and were in the early disease state. These estimates were obtained by smoothing the estimates of $A(0, t, Z_0)$ using an Epanechnikov kernel smoothing routine with a bandwidth of 2 years (See Gasser and Müller[11] (1979)). From these figures it appears that for young AML patients there is little evidence of a "cure", while for older patients there is some evidence that after about 10 years after transplantation the risk of death may have returned to the baseline population mortality rate. For young SAA patients it appears that their mortality rates are similar to those in the general population after about six years, while older SAA patients appear to have the same mortality rate at two years after transplant.

The above observations can be confirmed using the test described in the previous Section. To perform the test we set t equal to 12.6 years after transplant for AML and 12.4 years for SAA patients. These values were the times at which the last event occurred in the respective samples. For AML patients we test at $s = 8$ and 10 years if the mortality rate is the same for an AML patient as in the general population over the period $[s, t]$ using (2.10) for selected values of the covariates. The results are in Table 5. From this table we see that with the exception of old patients with early disease or old patients with no chronic GVHD and advanced disease the test rejects the hypothesis that the mortality rate has returned to normal over the period 8-12.6 years. For all patients over the interval 10-12.6 years there is no evidence that the mortality rate is different from the reference population.

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For SAA patients the results presented in Table 6 show a different pattern. Here it appears that for patients over age 16 with no adverse risk factors the mortality rate is the same as in the general population after two years post transplant. For patient over age 25 with a single risk factor (active GVHD, prior history of acute GVHD or late disease) their rate is the same as in the general population after 4 years, while if they have 2 or more risk factors the death rate is the same after 6 years. For young patients there is no difference between their mortality and the reference rates after 6 years if they have one of the risk factors present.

4 Discussion

The techniques discussed here for estimation of the relative mortality rate are simple extensions of the Cox proportional hazards model. They are extended to include left truncated data by a simple redefinition of the risk set. The assumption of a proportional effect of the covariates on the relative mortality can be tested by using a time dependent covariate approach as in the usual proportional hazards regression model.

The test statistic (2.11) has little power to detect a relative mortality rate which crosses one over the interval $[s, t]$. While it is mathematically possible that $\int_s^t \alpha_0(u)e^{\beta^t Z_0} du = (t - s)$ and $\alpha_0(u)e^{\beta^t Z_0} \neq 1$ for all $u \in [s, t]$, this would require that treated patients have a lower mortality rate than matched individuals in the general population. In most situations this is not biologically plausible.

As noted earlier these models have been suggested by other authors and estimates of $A(s, t, Z_0)$ are found in these papers. For this statistic the calculation of the variance of the estimator, requires some care since the estimator of $A(s, t, Z_0)$ does not have independent increments.

In looking at the results in Tables 5 and 6 there is an obvious multiple testing problem in performing tests at different time points and at multiple covariate values. One could argue that some type of a corrected significance level should be used to make the comparisons of interest. We choose not to do so since our goal is to provide the investigator with only a crude notion of when the patients mortality rate has returned to normal and the p-values computed serve as measures of evidence against this hypothesis.

The ability to determine whether and when the mortality rate of a transplant recipients returns to that of a normal population is important for several reasons. First, it can help guide stratigies for long-term medical follow-up of transplant recipients. Patient groups with persistently high mortality rates relative to the general population can be targeted for more frequent or intensive surveillance and study. Second, patients whose risk is similar to that of the general population can be reassured. This reassurance can significantly improve the quality of life for the transplant survivor. Finally, the convincing demonstration of risks similar to the general population may allow transplant survivors to obtain life and health

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insurance. This is currently a difficult and serious problem facing many transplant survivors.

Acknowledgements

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Table 1. Country Of Transplant For Study Patients

COUNTRY	SEX/RACE	AML	SAA
AUSTRALIA	MALE	67	28
	FEMALE	57	20
	TOTAL	124	48
BRAZIL	MALE	15	81
	FEMALE	12	42
	TOTAL	27	123
CANADA	MALE	60	31
	FEMALE	50	12
	TOTAL	110	43
DENMARK	MALE	11	9
	FEMALE	13	4
	TOTAL	24	13
ENGLAND (UK)	MALE	99	37
	FEMALE	88	26
	TOTAL	187	63
GERMANY	MALE	68	33
	FEMALE	62	22
	TOTAL	130	55
ITALY	MALE	53	18
	FEMALE	51	11
	TOTAL	104	29
JAPAN	MALE	18	15
	FEMALE	23	9
	TOTAL	41	24
NETHERLANDS	MALE	41	8
	FEMALE	35	6
	TOTAL	76	14
PORTUGAL	MALE	5	6
	FEMALE	5	1
	TOTAL	10	7
SPAIN	MALE	53	44
	FEMALE	52	25
	TOTAL	105	69
SWEDEN	MALE	27	14
	FEMALE	28	3
	TOTAL	55	17
USA	MALE/BLACK	8	14
	FEMALE/BLACK	13	7
	MALE/NON BLACK	232	119
	FEMALE/NON BLACK	241	84
	TOTAL	494	224
	TOTAL	1487	729

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Table 2. Frequencies of Covariates

COVARIATE	AML	SAA
Acute GVHD		
Yes	368 (24.7%)	145 (19.9%)
None	1119 (75.3%)	584 (80.1%)
Chronic Gvhd		
None	875 (58.8%)	465 (63.8%)
Resolved By 2 Years	236 (15.9%)	81 (11.1%)
Active At 2 Years	376 (25.3%)	183 (25.1%)
Age		
<16 Years	332 (22.4%)	284 (39.0%)
16-25 Years	350 (23.5%)	251 (34.4%)
>25 Years	805 (54.1%)	194 (26.6%)
Disease Stage		
Early	1132 (75.1%)	
Intermediate	162 (10.9%)	642 (88.1%)
Advanced	193 (13.0%)	87 (11.9%)

Table 3. Results Of Standard Cox Regression Analysis

Risk Factor	AML			SAA		
	$\hat{\beta}$	SE	p	$\hat{\beta}$	SE	p
Acute GVHD						
Yes	0.270	0.176	0.125	1.029	0.349	0.003
Chronic GVHD			0.0868[1]			0.001[1]
Resolved	0.295	0.224	0.188	0.592	0.616	0.337
Active	0.398	0.185	0.032	1.468	0.408	>0.001
Age			0.0834[1]			0.958[1]
16-25	0.141	0.260	0.588	-0.084	0.395	0.831
>25	0.438	0.224	0.050	0.032	0.424	0.940
Disease Stage			< 0.001[1]			
Intermediate	0.607	0.224	0.007			
Advanced	0.647	0.200	0.001	1.117	0.380	0.003

1. Two degree of freedom Wald test of effect of factor on survival.

Table 4. Results Of Relative Mortality Regression Analysis

Risk Factor	AML $\hat{\beta}$	AML SE	AML p	SAA $\hat{\beta}$	SAA SE	SAA p
Acute GVHD						
Yes	0.241	0.175	0.170	1.351	0.396	<0.001
Chronic GVHD			0.0678[1]			.003[1]
Resolved	0.300	0.225	0.182	0.468	0.626	0.454
Active	0.414	0.183	0.023	1.344	0.407	0.001
Age			<0.001[1]			<0.001[1]
16-25	-0.716	0.260	0.006	-0.863	0.395	0.029
>25	-1.339	0.224	<0.001	-1.614	0.426	<0.001
Disease Stage			0.003[1]			
Intermediate	0.666	0.224	0.003			
Advanced	0.463	0.201	0.021	1.168	0.360	0.001

1. Two degree of freedom Wald test of effect of factor on survival.

Table 5. p-Values Of The Test That The Mortality Rate For A Transplanted Patient Is The Same As In The General Population Over The Interval [s,12.6] For An AML Patient Without Acute GVHD

Age	Chronic GVHD	Disease stage	p-value when s=8	p-value when s=10
<16	None	Early	0.0118	0.2594
16-25	None	Early	0.0370	0.3917
>25	None	Early	0.1631	0.6360
<16	Active	Early	0.0078	0.2222
16-25	Active	Early	0.0177	0.3016
>25	Active	Early	0.0581	0.4570
<16	None	Intermediate	0.0064	0.2070
16-25	None	Intermediate	0.0125	0.2655
>25	None	Intermediate	0.0338	0.3796
<16	Active	Intermediate	0.0051	0.1899
16-25	Active	Intermediate	0.0081	0.2259
>25	Active	Intermediate	0.0116	0.2943
<16	None	Advanced	0.0075	0.2188
16-25	None	Advanced	0.0165	0.2935
>25	None	Advanced	0.0519	0.4399
<16	Active	Advanced	0.0057	0.1973
16-25	Active	Advanced	0.0098	0.2428
>25	Active	Advanced	0.0229	0.3306

Table 6. p-Values Of The Test That The Mortality Rate For A Transplanted Patient Is The Same As In The General Population Over The Interval [s,12.4] For An Aplastic Anemia Patient

Age	Chronic GVHD	Disease State	Acute GVHD	p-value when s=2	p-value when s=4	p-value when s=6	p-value when s=8
<16	None	Early	No	0.0011	0.0843	0.3641	0.4244
16-25	None	Early	No	0.1561	0.7968	0.9534	0.9207
>25	None	Early	No	0.9985	1.0000	1.0000	1.0000
<16	Active	Early	No	<0.0001	0.0051	0.0749	0.1459
16-25	Active	Early	No	0.0001	0.0232	0.1810	0.2623
>25	Active	Early	No	0.0048	0.1910	0.5454	0.5691
<16	None	Late	No	<0.0001	0.0064	0.0859	0.1597
16-25	None	Late	No	0.0003	0.0359	0.2308	0.3093
>25	None	Late	No	0.0133	0.3195	0.6865	0.6800
<16	Active	Late	No	<0.0001	0.0021	0.0440	0.1031
16-25	Active	Late	No	<0.0001	0.0037	0.0615	0.1283
>25	Active	Late	No	<0.0001	0.0099	0.1107	0.1888
<16	None	Early	Yes	0.0039	0.0234	0.0982	0.1610
16-25	None	Early	Yes	0.0102	0.0610	0.2054	0.2736
>25	None	Early	Yes	0.0481	0.2453	0.5350	0.5602
<16	Active	Early	Yes	0.0023	0.0130	0.0611	0.1151
16-25	Active	Early	Yes	0.0030	0.0174	0.0774	0.1360
>25	Active	Early	Yes	0.0049	0.0296	0.1180	0.1836
<16	None	Late	Yes	0.0023	0.0135	0.0632	0.1178
16-25	None	Late	Yes	0.0032	0.0191	0.0835	0.1434
>25	None	Late	Yes	0.0059	0.0354	0.1359	0.2031
<16	Active	Late	Yes	0.0020	0.0112	0.0540	0.1055
16-25	Active	Late	Yes	0.0021	0.0123	0.0583	0.1113
>25	Active	Late	Yes	0.0025	0.0147	0.0675	0.1234

Relative Mortality For AML Patients
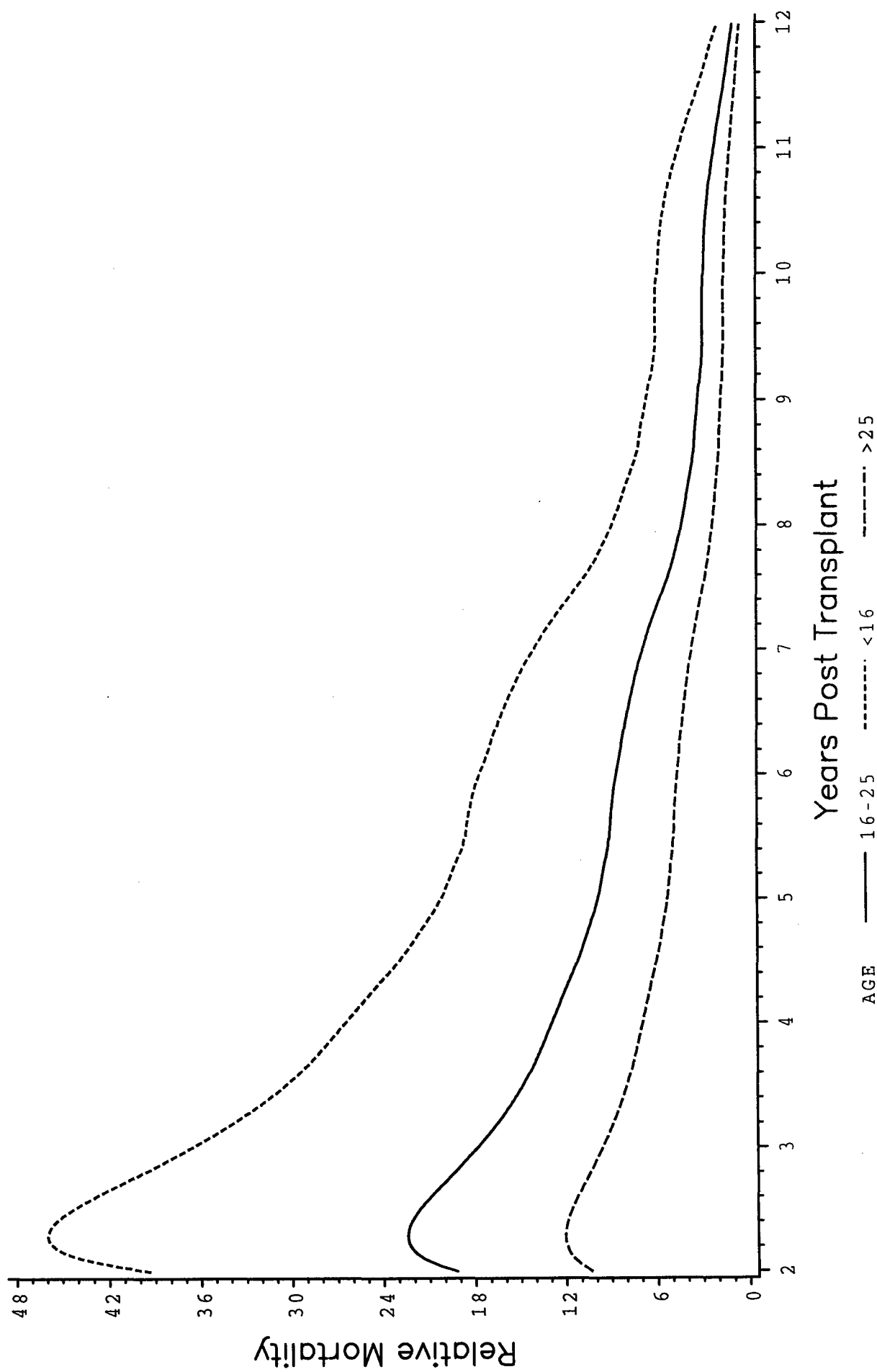
Figure 1

Relative Mortality For Aplastic Anemia Patients
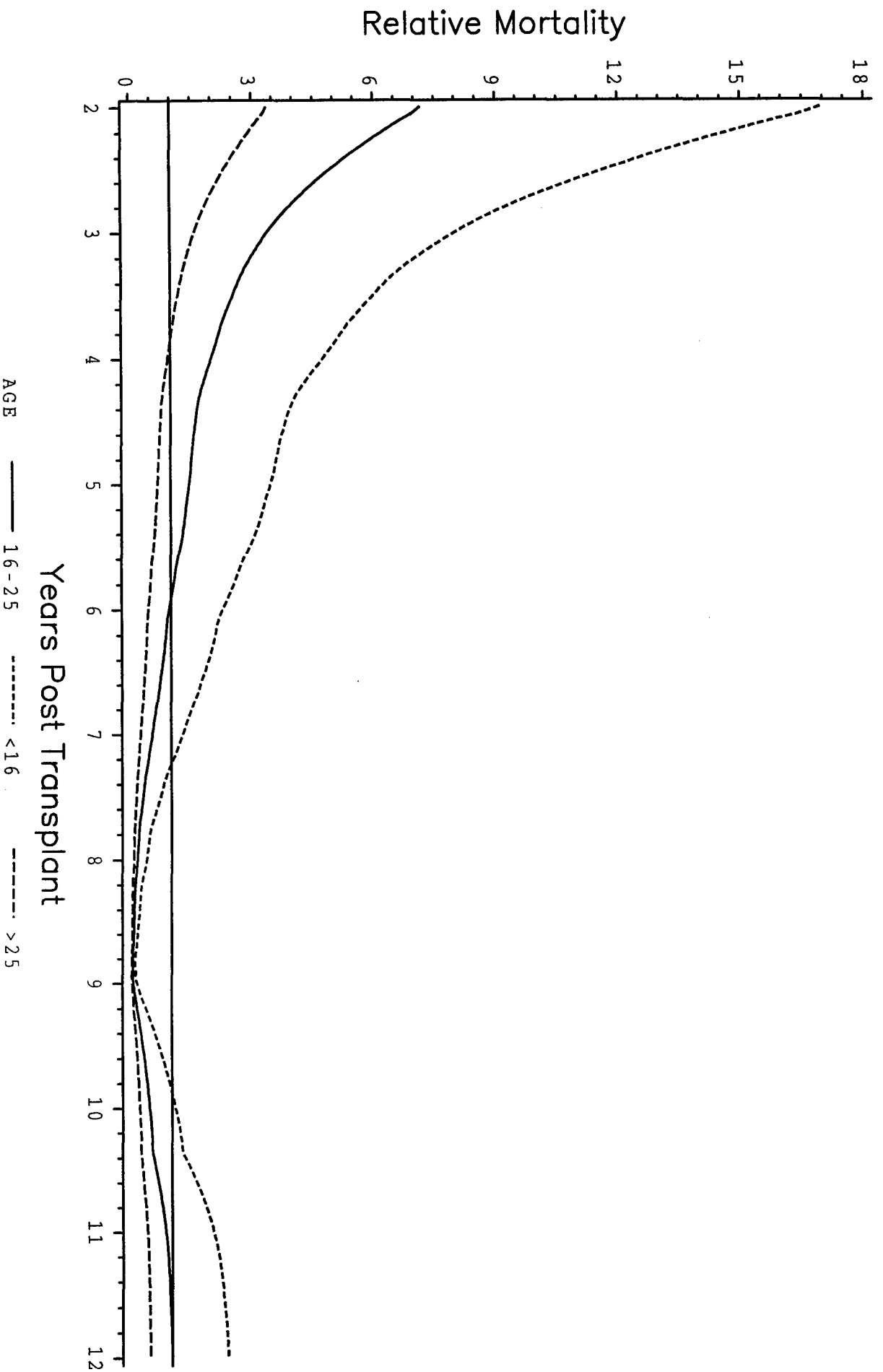
Figure 2

DETERMINING WHEN THE SURVIVAL RATES OF TWO TREATMENTS ARE THE SAME BASED ON A CENSORED DATA REGRESSION MODEL

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Determining When The Survival Rates Of Two Treatments Are The Same Based On A Censored Data Regression Model

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Abstract

Often when comparing the survival rates of individuals given either of two treatments the analysis stops with a test of the hypothesis of no treatment difference and perhaps a plot of the two survival functions. The hypothesis test is usually a comparison of the two survival curves over the entire observational period. An alternative approach to this problem is to provide an investigator with a confidence set for the set of times at which the survival rates of the two treatments are the same. We discuss how such confidence sets can be constructed when the proportional hazards or additive regression model is used to adjust the comparison of interest for other factors which may influence survival. These approaches are illustrated on retrospective data gathered to compare the survival rates of allogeneic and autologous bone marrow transplants for acute leukemia.

1 Introduction

A common problem arising in biomedical applications is the comparison of the survival functions or hazard rates of two treatments. Most standard statistical tests are based on comparing the survival curves or equivalently the hazard functions over a given time period. The time period considered is typically the period from initiation of the treatment to some point in time where observation of the patients ceases. This comparison may be made by the log rank test (cf. Andersen et al. 1993), for example, when there are no other covariates that may influence survival. When there are other covariates that may affect outcome in addition to the treatments under consideration, testing of treatment effects is carried out by some type of regression technique. These tests may be based on any number of parametric or semi-parametric models, but most common are tests based on either the Cox (1972) proportional hazards model or on Aalen's (1989, 1993) addative hazards model.

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The results of these analyses tell the investigator whether the two treatments have the same survival rates or not. When the results of the test indicate that the survival curves are different the natural question posed by most clinicians is "At what times are these two treatments different?" The answer to this question is crucial to a patient and physician in deciding which of the two treatments to use. It is of special importance when one treatment has higher early survival but lower long term survival. This question is of particular interest in applications like bone marrow transplantation where, when comparing disease free survival rates, one procedure may have a higher early mortality rate due to treatment toxicity than the other treatment but among survivors of this early period the relapse rate is lower.

In this note we present methods for constructing a confidence set for the times at which the two treatments have the same survival function based on Aalen's additive hazards model. Confidence sets for the times at which one treatment has a survival probability at least as high as the other treatment are also presented. The confidence sets are found by inverting a test that compares the survival rates for the two treatments at fixed points in time. The set of all times for which this test accepts the hypothesis of no treatment difference provides the desired confidence set. Note that the confidence set is based on a comparison of the survival rates or cumulative hazard rates at fixed points in time as opposed to the usual tests which compare survival for the entire curve.

The random sets, C_α that we construct by this technique are in fact conservative $(1 - \alpha) \times 100\%$ confidence sets for the set, Θ, of all times at which the two survival functions are the same. To see this consider the probability that Θ is a subset of C_α. Let t be an element of Θ. For such a t the subset of the sample space for which this t will also be in the set A_α has probability $(1 - \alpha)$ by our method of construction. This will be true for any t in Θ, however different t's yield different subsets of the sample space. The coverage probability is the probability of the union of theses different subsets as indexed by t in Θ. Since each subset has probability exactly $(1 - \alpha)$ our coverage probability must be at least $(1 - \alpha)$.

In the next section we review results from Klein and Zhang (1997) for comparing two treatments, when an adjustment for other covariates is needed, using the Cox (1972) proportional hazards model. We review both the case where there is no interaction between these other covariates and the main treatment comparison and the case where there is an interaction between the main treatment effect and some of the covariates. In this section the confidence sets are based on a stratified Cox regression model.

In section 3 we show how Aalen's additive model can be used to generate these confidence sets. Here the sets are based on fitting the full additive model to the data and inverting a pointwise test that the regression function for treatment is equal to zero.

In Section 4 we present an example of these confidence sets using data from The International Bone Marrow Transplant Registry and The Autologous Blood And Marrow Registry. The primary comparison of interest is between the leukemia free survival rates of autologous and allogeneic bone marrow transplants for acute leukemia patients. Autologous transplants, where a patient's own marrow is used to re grow their immune system, are typically less toxic then allogeneic transplants where the marrow from an HLA matched sibling is used. Patients do not experience graft-versus-host disease which is a leading contributor to death in

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the first several months after transplant. It is well known, however, that graft-versus-host disease has some protective effect against the reoccurrence of the leukemia, so allogeneic patients who survive the initial period tend to have lower leukemia relapse rates, off setting their higher early treatment related mortality. For a patient there is thus a trade off between early high mortality with allogeneic transplants and lower reoccurrence rates. To help in deciding between these two competing treatment modalities a confidence set for the times at which the survival probabilities of the two treatments are the same is of interest. Also, since autologous transplants are easier to perform as no donor is needed, a confidence set for those times where the survival probability for a autologous transplant patient is not smaller than the corresponding survival probability for an allogeneic transplant patient is also of interest.

2 Confidence Set Based On Cox's Proportional Hazards Model

2.1 Introduction

The Cox (1972) proportional hazards model has found wide acceptance as a tool for making comparisons between treatments adjusting for other covariates. Recently, Klein and Zhang (1997), have shown how this model can be used to construct confidence regions for times at which the survival functions are the same for the two treatments. Their approach, summerized in the next two subsections, is to perform a series of pointwise tests of the hypotheses of no difference in conditional cumulative hazard rates between the two treatments. They model the two cumulative hazards by a proportional hazards model stratified on treatment.

2.2 Adjustment For Covariates Not Confounded With Outcome

Let $Z = (Z_1, \cdots, Z_p)$ be a vector of fixed time covariates that influence survival. We assume that there is no significant interaction between the comparison of interest (treatment) and any of these covariates. Here we fit a proportional hazards model for the explanatory covariates stratifying on the treatment of interest. That is we fit the model

$$\lambda(t|Z, \text{Treatment}) = \begin{cases} \lambda_{10}(t)\exp\{\beta^T Z\}, & \text{for treatment 1,} \\ \lambda_{20}(t)\exp\{\beta^T Z\}, & \text{for treatment 2.} \end{cases} \tag{1}$$

Let $\hat{\beta}$ and $I(\hat{\beta})$ be the partial maximum likelihood estimator and the observed information for this model. An estimator of the baseline cumulative hazard rate for treatment j, $j = 1, 2$ is given by Breslow's (1975) estimator

$$\hat{\Lambda}_{j0}(t) = \int_0^t \frac{dN_j(u)}{S_j^{(0)}(\hat{\beta}, u)}, \quad \text{where} \tag{2}$$

$$S_j^{(0)}(\hat{\beta}, u) = \sum_{i=1}^n Y_{ij}(u)\exp\{\beta^T Z_i\} \tag{3}$$

with $Y_{ij}(u)$ the indicator of whether the ith individual is at risk at time u and is in the jth group.

For an individual with a covariate vector $\boldsymbol{Z_0}$, the two treatments will have the same survival rate at time t_0 if $\Lambda(t|\boldsymbol{Z_0}, \text{Treatment 1}) = \Lambda(t|\boldsymbol{Z_0}, \text{Treatment 2})$, which from (1) is equivalent to having $\Lambda_{10}(t_0) = \Lambda_{20}(t_0)$ or $\Delta(t_0) = \Lambda_{20}(t_0) - \Lambda_{10}(t_0) = 0$. Note that this comparison is independent of the value of $\boldsymbol{Z_0}$. The test statistic for this hypothesis is

$$\hat{\Delta}(t_0) = \hat{\Lambda}_{20}(t_0) - \hat{\Lambda}_{10}(t_0). \tag{4}$$

The large sample variance of this statistic is (see Klein and Zhang (1997))

$$Var[\hat{\Delta}(t_0)] = \sum_{j=1}^{2} \int_0^{t_0} \frac{dN_j(u)}{[S_j^{(0)}(\hat{\beta}, u)]^2} + \boldsymbol{W}^T(\hat{\beta}, t_0)[I(\hat{\beta})]^{-1}\boldsymbol{W}(\hat{\beta}, t_0), \quad \text{where} \tag{5}$$

$$\boldsymbol{W}^T(\hat{\beta}, t_0) = \int_0^{t_0} \tilde{\boldsymbol{Z}}_2(\hat{\beta}, u)d\hat{\Lambda}_{20}(u) - \tilde{\boldsymbol{Z}}_1(\hat{\beta}, u)d\hat{\Lambda}_{10}(u),$$

$$\tilde{\boldsymbol{Z}}_j(\hat{\beta}, u) = \frac{S_j^{(1)}(\hat{\beta}, u)}{S_j^{(0)}(\hat{\beta}, u)}, \quad \text{and} \tag{6}$$

$$S_j^{(1)}(\hat{\beta}, u) = \sum_{i=1}^{n} Y_{ij}(u)\boldsymbol{Z}_i \exp\{\hat{\beta}^T \boldsymbol{Z}_i\}.$$

An α-level test of $H_o : \Delta(t_0) = 0$ versus $H_a : \Delta(t_0) \neq 0$ is accepted when $|\hat{\Delta}(t_0)/\sqrt{Var[\hat{\Delta}(t_0)]}| \leq z_{\alpha/2}$, where z_α is the αth upper quantile of a standard normal random variable. Inverting this test yields a $100 \times (1 - \alpha)$ confidence set for the times at which $S_1(t) = S_2(t)$ as

$$\left\{ t_0 : -z_{\alpha/2} \leq \hat{\Delta}(t_0)/[Var(\hat{\Delta}(t_0))]^{1/2} \leq z_{\alpha/2} \right\}$$

$$= \left\{ t_0 : \hat{\Delta}(t_0) - z_{\alpha/2}\sqrt{Var(\hat{\Delta}(t_0))} \leq 0 \leq \hat{\Delta}(t_0) + z_{\alpha/2}\sqrt{Var(\hat{\Delta}(t_0))} \right\} \tag{7}$$

To find sets of time where we are $(1 - \alpha) \times 100\%$ confident that $S_1(t) \leq S_2(t)$ consider testing the hypothesis $H_0 : \Lambda_1(t_0) \geq \Lambda_2(t_0)$ versus $H_A : \Lambda_1(t_0) < \Lambda_2(t_0)$. This is equivalent to testing $H_0 : \Delta(t_0) \leq 0$ versus $H_A : \Delta(t_0) > 0$. The desired confidence set for those points in time where treatment 2 is at least as good as treatment 1 ($\Delta(t_0) \leq 0$) is given by

$$\left\{ t_0 : \hat{\Delta}(t_0)/\sqrt{Var[\hat{\Delta}(t_0)]} < z_\alpha \right\} = \left\{ t_0 : 0 \geq \hat{\Delta}(t_0) - z_\alpha\sqrt{Var[\hat{\Delta}(t_0)]} \right\}.$$

2.3 Adjustment For Covariates Confounded With Outcome

In some instances the comparison of the treatments of interest is complicated by some of the explanatory covariates have differential effects on the survival rates for the two treatments. Suppose that the covariate vector can be partitioned as $\boldsymbol{Z}^T = (\boldsymbol{Z}_1^T, \boldsymbol{Z}_2^T)^T$, where $\boldsymbol{Z}_1$ is a

vector of length q_1 of the covariates confounded with treatment and Z_2 is a vector of length q_2 of the covariates not confounded with treatment.

To construct the confidence set where the survival rates are the same for the two treatments a stratified proportional hazards model is used. We fit the model

$$
\lambda(t|\boldsymbol{Z}, \text{Treatment}) = \begin{cases} \lambda_{10}(t) \exp\{\gamma_1^T \boldsymbol{Z}_1 + \theta^T \boldsymbol{Z}_2\}, & \text{for treatment 1,} \\ \lambda_{20}(t) \exp\{\gamma_2^T \boldsymbol{Z}_1 + \theta^T \boldsymbol{Z}_2\}, & \text{for treatment 2.} \end{cases} \tag{8}
$$

Estimates for $\beta = (\theta_1^T, \gamma_1^T, \gamma_2^T)$ are found by fitting a Cox model, stratified on treatment group to the data with an augmented covariate vector $\boldsymbol{Z}^T = (\boldsymbol{Z}_2^T, \boldsymbol{Z}_1^T I[\text{Treatment} = 1], \boldsymbol{Z}_1^T I[\text{Treatment} = 2])$. For a given set of confounding factors, $\boldsymbol{Z}_{10}$, the two treatments will have the same survival rate at time t_0 if

$$
\Delta(t_0|\boldsymbol{Z}_{10}) = \Lambda_{20}(t_0) \exp\{\gamma_2^T \boldsymbol{Z}_{10}\} - \Lambda_{10}(t_0) \exp\{\gamma_1^T \boldsymbol{Z}_{10}\} \tag{9}
$$

is equal to zero. The estimator of $\Delta(t_0|\boldsymbol{Z}_{10})$ given by

$$
\hat{\Delta}(t_0|\boldsymbol{Z}_{10}) = \hat{\Lambda}_{20}(t_0) \exp\{\hat{\gamma}_2^T \boldsymbol{Z}_{10}\} - \hat{\Lambda}_{10}(t_0) \exp\{\hat{\gamma}_1^T \boldsymbol{Z}_{10}\}
$$

follows from the fitted Cox model with $\Lambda_{j0}()$ estimated using Breslow's estimator (2).

An estimator of the asymptotic variance of $\hat{\Delta}(t_0|\boldsymbol{Z}_{10})$ is (see Klein and Zhang (1997))

$$
Var(\hat{\Delta}(t_0|\boldsymbol{Z}_{10})) = \sum_{j=1}^{2} \int_0^{t_0} \exp\{2\hat{\gamma}_j^T \boldsymbol{Z}_{10}\} \frac{dN_j(u)}{[S_j^{(0)}(\hat{\beta}, u)]^2} +
$$
$$
+ \left\{\boldsymbol{W}_2(\hat{\beta}, t_0) - \boldsymbol{W}_1(\hat{\beta}, t_0)\right\}^T [I(\hat{\beta})]^{-1} \left\{\boldsymbol{W}_2(\hat{\beta}, t_0) - \boldsymbol{W}_1(\hat{\beta}, t_0)\right\}
$$

Here

$$
\boldsymbol{W}_j(\hat{\beta}, t_0) = \exp\{\hat{\gamma}_j^T \boldsymbol{Z}_{10}\} \int_0^{t_0} [\tilde{\boldsymbol{Z}}_j(\hat{\beta}, u) - \boldsymbol{Z}_{(j)}] d\hat{\Lambda}_{j0}(u), \quad j = 1, 2
$$

with $\tilde{\boldsymbol{Z}}_j(\hat{\beta}, u)$, defined by (6) and $\boldsymbol{Z}_{(1)} = (\boldsymbol{0}^T, \boldsymbol{Z}_{10}^T, \boldsymbol{0}^T)$ and $\boldsymbol{Z}_{(2)} = (\boldsymbol{0}^T, \boldsymbol{0}^T, \boldsymbol{Z}_{10}^T)$.

Since at t_0 an α level test of the equality of the two survival functions for a fixed value $\boldsymbol{Z}_{10}$ of $\boldsymbol{Z}$ is accepted when $\hat{\Delta}(t_0|\boldsymbol{Z}_{10})/[Var(\hat{\Delta}(t_0|\boldsymbol{Z}_{10}))]^{1/2}$ is in the interval $[-z_{\alpha/2}, z_{\alpha/2}]$, a $(1 - \alpha) \times 100\%$ confidence set for those times at which the two treatments are not different is given by

$$
\left\{t : -z_{\alpha/2} \leq \hat{\Delta}(t_0|\boldsymbol{Z}_{10})/[Var(\hat{\Delta}(t_0|\boldsymbol{Z}_{10}))]^{1/2} \leq z_{\alpha/2}\right\}
$$

Similarly a confidence set for those points in time where treatment 2 is at least as good as treatment 1 is given by

$$
\left\{t : \hat{\Delta}(t_0|\boldsymbol{Z}_{10})/[Var(\hat{\Delta}(t_0|\boldsymbol{Z}_{10}))]^{1/2} \leq z_{\alpha}\right\}
$$

3 Confidence Sets Based On The Additive Hazards Model

3.1 Estimation In The Additive Model

An alternative to the proportional hazards model is the additive hazards model first suggested by Aalen (1980). This model allows for covariate effects which vary over time since the regression coefficients are functions of time as opposed to the Cox model where they are constants. This approach uses a linear model for the conditional hazard rate and estimates regression coefficient functions by a least squares technique.

To define the model suppose we have an individual with covariates $Z_1(t), \cdots, Z_p(t)$. For such an individual the model for the conditional hazard rate is given by

$$
\lambda(t|Z_1(t), \cdots, Z_p(t)) = \begin{cases} \alpha_0(t) + \sum_{k=1}^{p} \alpha_k(t) Z_k(t) & \text{if this individual is at risk at time } t, \\ 0 & \text{otherwise.} \end{cases}
$$

Here the $\alpha_j(t)$'s, $j = 0, \cdots, p$, are functions of time to be estimated form the data.

Suppose we observe n individuals. Associated with each individual is a p-vector of possibly time dependent covariates, $\boldsymbol{Z}_i(t) = (1, Z_i(t), \cdots, Z_p(t))$. (Here the first element of the covariate vector is 1 to allow for a baseline intensity.) Let $\lambda_i(t)$ denote the intensity at which the event occurs for the ith subject. To write the model in matrix notation let $\boldsymbol{Y}(t)$ be the $n \times (p + 1)$ matrix whose ith row is $\boldsymbol{Z}_i(t)$ if individual i is at risk at time t and is a row of zeros if this subject is not at risk at time t. Then the additive regression model is

$$
\boldsymbol{\lambda}(t) = \boldsymbol{Y}(t) \boldsymbol{\alpha}(t). \tag{10}
$$

Here the first element of $\boldsymbol{\alpha}(t)$ is a baseline intensity and the remaining elements are the regression functions which describe the effect of the covariate over time on survival.

The only restriction on covariates which can be used in this model is that they are predictable in the sense that their value is known just prior to time t (cf. Aalen 1978). In the data set to be used here to illustrate these techniques all covariates are known at the time of transplant so this condition is satisfied.

Estimation for the additive model is based on a least squares approach. Direct estimation of $\boldsymbol{\alpha}(t)$ is difficult so we estimate instead the cumulative regression function, $\boldsymbol{A}(t) = (A_1(t), \ldots, A_p(t))^T$, where

$$
A_j(t) = \int_0^t \alpha_j(t) dt, \qquad j = 0, 1, \cdots, p.
$$

Let $T_1 < T_2 < \ldots$ be the ordered observed times at which events occur. Then Aalen (1980, 1989) shows that the least squares estimator of $\boldsymbol{A}(t)$ is given by

$$
\hat{\boldsymbol{A}}(t) = \sum_{T_k \leq t} \boldsymbol{X}(T_k) \boldsymbol{I}_k, \qquad \text{where} \tag{11}
$$

$X(t)$ is a generalized inverse of $Y(t)$, and I_k is the n-vector of whose ith element is 1 if subject i experiences the event at time T_k and is 0 if they don't. The estimator (11) is only defined over the range where the matrix $Y(t)$ is of full rank. Let τ be the random point in time where $Y()$ loses its full rank.

Any generalized inverse can be used in computing the estimator (10). By analogy to the usual linear models analysis we shall use the generalized inverse suggested by Aalen (1980), Huffer and McKeague (1991), McKeague (1988), namely

$$X(t) = (Y(t)^T Y(t))^{-1} Y(t)^T \tag{12}$$

An alternative choice of the generalized inverse is a weighted inverse which leads to the analog of a weighted least squares estimate (See Huffer and McKeague (1991), McKeague (1988)).

The variance matrix of $\hat{A}(t)$ can be estimated consistently by

$$\Sigma(t) = \sum_{T_k} X(T_k) D_k X(T_k)^T, \tag{13}$$

where D is the diagonal matrix with I_k as the diagonal. One can show (cf. Aalen 1980, Andersen et al (1993)) that $\hat{A}(t)$ converges weakly to a Gaussian process with independent increments under a wide set of regularity conditions. A SAS Macro to perform the calculations need to obtain $\hat{A}(t)$ and $\Sigma(t)$ is described in Howell and Klein (1996).

3.2 Confidence Sets Adjusted For Other Covariates Not Confounded With Treatment

As for the proportional hazards model, to find a confidence set for those times where the two treatments are the same adjusting for a p-variate set of covariates $Z_1, ..., Z_p$, we base the set on a series of pointwise tests of equality of the adjusted cumulative hazard rates for the two treatments. For each individual define the $p+2$ dimensional vector $Z_i(t) = (1, Z_1(t), ..., Z_p(t), W)$, where $W = 1$ if this individual received treatment 2 and 0 otherwise. Using this coding of the covariates we compute $\hat{A}(t)$ and $\Sigma(t)$. Now the difference in cumulative hazard rates between an individual given treatment 2 and an individual given treatment 1 is

$$
\begin{aligned}
\Delta(t|Z) &= \Lambda(t|Z, \text{ Treatment 2}) - \Lambda(t|Z, \text{ Treatment 1}) \\
&= \left\{ A_0(t) + \sum_{k=1}^{p} A_k(t) Z_k(t) + A_{p+1}(t) \right\} - \left\{ A_0(t) + \sum_{k=1}^{p} A_k(t) Z_k(t) \right\} \\
&= A_{p+1}(t)
\end{aligned}
$$

The variance of this estimator is found directly from $\Sigma(t)$.

An α-level test of $H_o : \Delta(t_0) = 0$ versus $H_a : \Delta(t_0) \neq 0$ is accepted when $|\hat{\Delta}(t_0)/\sqrt{Var[\hat{\Delta}(t_0)]}| \leq z_{\alpha/2}$, where z_α is the αth upper quantile of a standard normal random

variable. Inverting this test yields a $100 \times (1 - \alpha)$ confidence set for the times at which $S_1(t) = S_2(t)$ as

$$\left\{ t_0 : -z_{\alpha/2} \leq \hat{\Delta}(t_0) / [Var(\hat{\Delta}(t_0))]^{1/2} \leq z_{\alpha/2} \right\}$$

$$= \left\{ t_0 : \hat{\Delta}(t_0) - z_{\alpha/2}\sqrt{Var(\hat{\Delta}(t_0))} \leq 0 \leq \hat{\Delta}(t_0) + z_{\alpha/2}\sqrt{Var(\hat{\Delta}(t_0))} \right\} \qquad (14)$$

To find sets of time where we are $(1 - \alpha) \times 100\%$ confident that $S_1(t) \leq S_2(t)$ consider testing the hypothesis $H_0 : \Lambda_1(t_0) \geq \Lambda_2(t_0)$ versus $H_A : \Lambda_1(t_0) < \Lambda_2(t_0)$. This is equivalent to testing $H_0 : \Delta(t_0) \leq 0$ versus $H_A : \Delta(t_0) > 0$. The desired confidence set for those points in time where treatment 2 is at least as good as treatment 1 $(\Delta(t_0) \leq 0)$ is given by

$$\left\{ t_0 : \hat{\Delta}(t_0) / \sqrt{Var[\hat{\Delta}(t_0)]} < z_\alpha \right\} = \left\{ t_0 : 0 \geq \hat{\Delta}(t_0) - z_\alpha\sqrt{Var[\hat{\Delta}(t_0)]} \right\}.$$

3.3 Confidence Sets When The Covariates Are Confounded With Treatment

Suppose that the covaraites vector can be partitioned into as a set Z_1 of dimension q_1 of covariates confounded with treatment and a set Z_2 of dimension q_2 of covariates not confounded with treatment. For this case we define for each individual the $q_2 + 2q_1 + 2$ dimensional vector $Z_i(t) = (1, Z_2, WZ_1, [1 - W]Z_1, W)$. Here W is again the indicator of an individual being in treatment group 2. Note that for this covariate vector we have the following cumulative hazard rates for the two treatment groups:

Treatment 2: $A_0(t) + \sum_{k=1}^{q_2} A_k(t)Z_{2k}(t) + \sum_{k=1}^{q_1} A_{1+q_2+k}(t)Z_{1k}(t) + A_{2+2q_1+q_2}(t)$

Treatment 1: $A_0(t) + \sum_{k=1}^{q_2} A_k(t)Z_{2k}(t) + \sum_{k=1}^{q_1} A_{1+q_1+q_2+k}(t)Z_{1k}(t)$

For an individual with a set Z_{10} of covariates for Z_1, the survival functions will be the same at time t if these two cumulative hazard rates are the same. That is if

$$\Delta(t|Z_{10}) = A_{2+2q_1+q_2}(t) + \sum_{k=1}^{q_1} [A_{1+q_2+k}(t) - A_{1+q_1+q_2+k}(t)]Z_{1k}(t) = 0.$$

Note that if we let $C = (0, Z_{10}, -Z_{10}, 1)$, where 0 is the $q_2 + 1$ vector of zero's then $\Delta(t|Z_{10}) = CA(t)$ and the variance of $\hat{\Delta}(t|Z_{10}) = C\hat{A}(t)$ is estimated by $C\Sigma(t)C^T$.

Since at t_0 an α level test of the equality of the two survival functions for a fixed value of Z_1 is accepted when $\hat{\Delta}(t_0|Z_{10}) / [Var(\hat{\Delta}(t_0|Z_{10}))]^{1/2}$ is in the interval $[-z_{\alpha/2}, z_{\alpha/2}]$, a $(1 - \alpha) \times 100\%$ confidence set for those times at which the two treatments are not different is given by

$$\left\{ t : -z_{\alpha/2} \leq \hat{\Delta}(t_0|Z_{10}) / [Var(\hat{\Delta}(t_0|Z_{10}))]^{1/2} \leq z_{\alpha/2} \right\}$$

Similarly a confidence set for those points in time where treatment 2 is at least as good as treatment 1 is given by

$$\left\{ t : \hat{\Delta}(t_0|Z_{10}) / [Var(\hat{\Delta}(t_0|Z_{10}))]^{1/2} \leq z_\alpha \right\}$$

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4 Example

To illustrate these calculations we consider data from a retrospective study of the effectiveness of bone marrow transplantation for patients with acute myelocytic leukemia (AML). Of interest is the comparison of survival rates between patients given either an autologous (auto) or allogeneic (allo) transplant. The data set consists of data on 1,325 patients reported over a four year period to either the International Bone Marrow Transplant Registry (allo transplants) or the Autologous Blood and Marrow Registry (auto transplants). 381 patients received an autologous transplant and 944 a HLA identical sibling allogeneic transplant.

The comparison of interest is between the leukemia free survival times (LFS) of the two groups. A patient is considered as an event if they die or their leukemia returns. The event time is the smaller of the time of relapse or death. Figure 1 shows the unadjusted Kaplan-Meier estimators for the two treatment groups. The log rank test of equality of the survival functions in the two treatment groups is rejected with a p-value of 0.007.

In addition to type of transplant, data on each patient includes remission status (1st or second complete remission), age (dichotomized as ≤ 30 or > 30) and Karnofsky score (dichotomized as < 90 or ≥ 90) at transplant. For patients in second complete remission the duration of the first complete remission is also recorded(dichotomized as ≤ 1 yr or > 1 yr). We wish to determine when the two types of transplants have the same survival rate after adjustment for these fixed explanatory covariates.

We first assume that there is no interaction between these covariates and the type of transplant. For the proportional hazards approach a Cox model is fit, stratified on transplant type, with binary covariates for remission status, age, Karnofsky score and duration of first complete remission. Applying the results in Section 2.2 we find that a 95% confidence set for the times where the survival probabilities for the two transplant types are not different, adjusted for this set of covariates, is the set of time points given by

$$C2 = \{t_0 |\ t_0 \in [0, 0.132) \cup [0.151, 1.242) \cup [2.281, 2.418)\}\ \text{years}.$$

A 95% confidence set for those times where patients given an auto transplant have a survival probability at least as high as patients given an allo transplant is given by

$$C1 = \{t_0 |\ t_0 \in [0, 0.861) \cup [0.872, 1.179)\}\ \text{years}.$$

For the additive model discussed in Section 3.2 we fit the model with covariates for type of transplant and for the four fixed covariates. The 95% confidence set for the times where the survival probabilities for the two transplant types are not different based on this model is given by

$$C2 = \{t_0 |\ t_0 \in [0, 0.137) \cup [0.143, 0.855) \cup [0.880, 1.102) \cup [1.124, 1.1662)\}\ \text{years}.$$

The 95% confidence set for those times where patients given an auto transplant have a survival probability at least as high as patients given an allo transplant based on the additive

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model is given by

$$C1 = \{t_0|\ t_0 \in [0, 0.526) \cup [0.534, 0.537) \cup [0.611, 0.641)$$
$$\cup [0.688, 0.726) \cup [0.732, 0.768) \cup [0.959, 0.984)\}\ \text{years}.$$

The sets $C1$ suggest that for a period of time after transplant auto patients do not do any worse then allo patients, but after this period they have smaller survival probabilities. This time interval is estimated to be a little over a year based on the proportional hazards model and a little under a year based on the additive model.

The above intervals assumed that the fixed covariates were not confounded with treatment. However, in this study, based on either the proportional hazards or additive hazards model, it appears that age has a differential effect on the two types of transplants.

To adjust for this confounding factor using the proportional hazards approach, a model stratified on type of transplant is fit to the covariates remission status, Karnofsky score, duration of first complete remission and two interaction covariates. The interaction covariates are $Z_{11} = 1$ if age > 30 and allo transplant and $Z_{12} = 1$ if age > 30 and auto transplant.

Using the results in Section 2.2, 95% confidence sets for the times (in years) where the two treatments have the same survival probability are

$$C2_{\leq 30} = \{t_0|t_0 \in [0, 1.242) \cup [2.349, 2.418)\}\ \text{years}.$$

for patients age 30 or less and

$$C2_{>30} = \{t_0|t_0 \in [0, 0.115) \cup [0.118, 0.129) \cup [0.1590, 5.891)\}\ \text{years}$$

for patients over age 30.

A 95% confidence set for those times where patients given an auto transplant have a survival probability at least as high as patients given an allo transplant based on the proportional hazards model is given by

$$C1_{\leq 30} = \{t_0|t_0 \in [0, 0.858) \cup [0.885, 1.162)\}\ \text{years}$$

for patients age 30 or less and

$$C1_{>30} = \{t_0|t_0 \in [0, 5.891)\}\ \text{years},$$

for patients over age 30.

For the additive model approach we fit a using a covariate vector with components remission status, Karnofsky score, duration of first complete remission, Z_{11}, $Z_{12} = 1$, and the indicator of type of transplant. Applying the results in Section 3.3 we find that 95% confidence sets for the times (in years) where the two treatments have the same survival probability based on the additive model are

$$C2_{\leq 30} = \{t_0|t_0 \in [0, 0.398) \cup [0.622, 0.632) \cup [0.696, 0.721) \cup [0.732, 0.855)$$
$$\cup [0.872, 1.242) \cup [1.672, 2.837) \cup [3.100, 5.052)\}\ \text{years}$$

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for patients age 30 or less and

$$C2_{>30} = \{t_0|t_0 \in [0, 0.066) \cup [0.159, 0.162) \cup [0.165, 0.167)$$
$$\cup [0.189, 0.195) \cup [0.197, 5.05)\} \text{ years}$$

for patients over age 30.

A 95% confidence set for those times where patients given an auto transplant have a survival probability at least as high as patients given an allo transplant based on the additive hazard model is given by

$$C1_{\leq 30} = \{t_0|t_0 \in [0, 0.356) \cup [2.059, 2.448) \cup [4.260, 5.052)\} \text{ years}$$

for patients age 30 or less and

$$C1_{>30} = \{t_0|t_0 \in [0, 1.8558) \cup [1.8722, 2.083) \cup [2.215, 2.418) \cup [3.753, 5.052)\} \text{ years}$$

for patients over age 30.

These intervals suggest that for older patients there is little if any advantage in survival for either type of transplant. For younger patients the proportional hazards model suggests that the survival rates are different after about two and a half years. Based on the one sided sets constructed by the additive hazard model, the inference for younger patients is that they have survival given an auto transplant at least as good as if they were given an allo transplant in the first 3 months after transplant, for a brief period in year two and then again after about 3 and three-fourth years.

5 Acknowledgments

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Figure 1. Kaplan-Meier Estimates Of Leukemia Free Survival
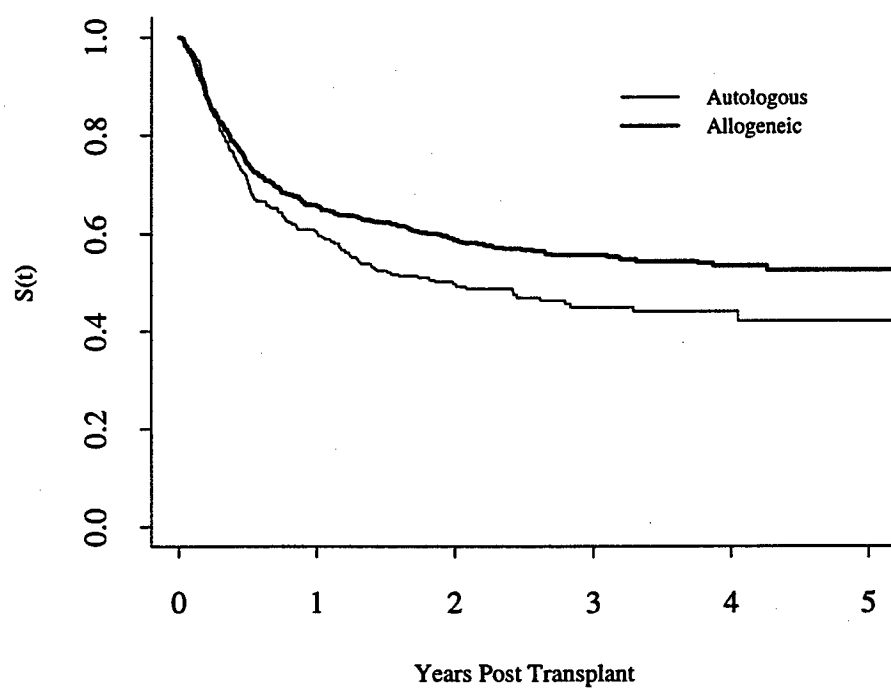
Autologous
Allogeneic

S(t)

Years Post Transplant

Confidence bands for the difference
of two survival curves under
proportional hazards model

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CONFIDENCE BANDS FOR THE DIFFERENCE OF TWO SURVIVAL CURVES UNDER PROPORTIONAL HAZARDS MODEL

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Abstract.

A common approach to testing for differences between the survival rates of two therapies is to use a proportional hazards regression model which allows for an adjustment of the two survival functions for any imbalance in prognostic factors in the comparison. An alternative approach to this problem is to plot the difference between the two predicted survival functions with a confidence band that provides information about when these two treatments differ. Such a band will depend on the covariate values of a given patient. In this paper we show how to construct a confidence band for the difference of two survival functions based on the proportional hazards model. A simulation approach is used to generate the bands. This approach is used to compare the survival probabilities of chemotherapy and allogeneic bone marrow transplants for chronic leukemia.

1. Introduction

A common problem encountered in biomedical applications is the comparison of the survival rates of two treatments. In this comparison one tests whether the two treatments have the same survival function or equivalently the same hazard function over a given time period. When there are additional covariates associated with survival then this testing is typically performed in the framework of a Cox (1972) proportional hazards model.

When the testing results indicate that two survival functions are different, patients and physicians often want to known "at what times are these two treatments different?". This is particularly important when one treatment has a higher early survival but lower long term survival. This question is of particular interest in comparing the survival rates of bone marrow transplantation (BMT) and conventional chemotherapy patients. Here, bone marrow transplantation patients may have a higher early mortality rate, due to treatment toxicity, and a lower late death rate, due to a reduced relapse risk.

To answer this question, it is useful to plot the estimate of the difference between the two survival functions along with a confidence band for the difference. Visually examining these

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plots and comparing the confidence bands with the zero line summarizes how the difference betwen the two survival functions change with time. Recently, Parzen *et al* (1997) used the Kaplan-Meier (1958) estimators of the two survival functions, $\hat{F}_1(\cdot)$ and $\hat{F}_2(\cdot)$, to estimate the difference between the survival functions and they proposed a simulation method to construct a confidence band for this difference.

In many applications there is a need, when comparing two treatments, to make adjustments for other covariates that may affect outcome. When the two treatments are found to have different survival rates then patients and physicians want to known "for a given patient with a certain set of covariates, when are the two treatments different?". In the sequal, we attempt to answer this question by comparing the estimated survival functions for the two treatments using a stratified Cox(1972) proportional hazards model. That is, we estimate the difference between the two conditional survival functions for a particular set of covariate values, $D(\cdot; z_0) = F_2(\cdot; z_0) - F_1(\cdot; z_0)$, by $\hat{D}(\cdot; z_0) = e^{-\hat{\Lambda}_2(\cdot; z_0)} - e^{-\hat{\Lambda}_1(\cdot; z_0)}$ where $\hat{\Lambda}_i(\cdot; z_0), i = 1, 2$ are the Breslow (1975) type estimate for the cumulative hazard functions.

To find a confidence band for $D(\cdot; z_0)$, using the martingale central limit theory one can show that $\hat{D}(\cdot; z_0)$ converges weakly to a zero mean Gaussian process. It is well known that this limiting Gaussian process does not have independent increments, hence, it is difficult to evaluate this limiting distribution analytically. In the one sample cases, Lin *et al* (1994) proposed a simulation method to construct the confidence bands for $F(\cdot; z_0)$. In this paper we propose to use a similar simulation method to construct a confidence band for $D(\cdot; z_0)$.

In Section 2, we present the estimates and simulation method used to construct a confidence band for the difference of two survival functions based on a stratified Cox proportional hazards model. In Section 3, we present an example of this technique using chronic leukemia data from The International Bone Marrow Transplant Registry and German CML Study Group.

2. Confidence bands for the difference of two survival functions

Let the observations on subject j of treatment group i be $\{X_{ij}, T_{ij}, D_{ij}, Z_{ij}\}$ where X_{ij} is the left-truncation time, $D_{ij} = 0$ if subject (i, j) is censored, $D_{ij} = 1$ otherwise, T_{ij} is the observation time of subject (i, j) which is observed only if $T_{ij} \geq X_{ij}$, and Z_{ij} are the covariates, for $i = 1, 2$ and $j = 1, \cdots, n_i$. So the data considered here are left-truncated and right censored. Note that if $X_{ij} = 0$ for all i, j then the data is right censored only. We fit a Cox (1972) model stratified on treatment. That is for a patient given treatment i, $i = 1, 2$, the hazard function is

$$\lambda_i(t; z) = \lambda_{i0}(t) e^{\beta' z},$$

where $\lambda_{i0}(t)$ is the baseline hazard functions for treatment i, z is a $p-$vector of covariates that influence survival, and β is a $p-$vector of unknown regression coefficients.

Here, β can be estimated by maximizing the stratified Cox partial log likelihood function

$$C(\beta, t) = \sum_{i=1}^{2} \sum_{j=1}^{n_i} \int_0^t \beta' Z_{ij} dN_{ij}(u) - \sum_{i=1}^{2} \int_0^t \log \left(\sum_{j=1}^{n_i} Y_{ij}(u) e^{\beta' Z_{ij}} \right) d\bar{N}_i(u),$$

where $N_{ij}(u) = I\{X_{ij} \leq T_{ij} \leq u, D_{ij} = 1\}$, $\bar{N}_i = \sum_i N_{ij}$, and $Y_{ij}(u) = I\{X_{ij} \leq u \leq T_{ij}\}$ is the indicator of whether the jth individual is at risk at time u and is in the ith treatment group. Note that an individual is at risk only since his or her truncation time, so that the size of the risk set is initally increasing and then decreases.

To compare two predicted survival curves, we estimate the conditional survival functions for the two treatments for a patient with a particular set of covariates z_0,

$$F_i(t; z_0) = P(T > t | z_0, \text{ Treatment } i) = e^{-\Lambda_i(t; z_0)},$$

where $\Lambda_i(t|z_0) = e^{\beta' z_0} \int_0^t \lambda_{i0}(u) du$. An estimator of the cumulative baseline hazard rate for treatment $i, i = 1, 2$ is given by Breslow's (1975) estimator

$$\hat{\Lambda}_{i0}(t) = \int_0^t \frac{d\bar{N}_i(u)}{\sum_{j=1}^{n_i} Y_{ij}(u) \exp(\hat{\beta}' Z_{ij})}.$$

For convenience we introduce the notations

$$
\begin{aligned}
S_i^{(k)}(\beta, t) &= \frac{1}{n_i} \sum_{j=1}^{n_i} Y_{ij}(t) Z_{ij}^{\otimes k} e^{\beta' Z_{ij}}, \\
E_i(\beta, t) &= S_i^{(1)}(\beta, t) / S_i^{(0)}(\beta, t), \\
V_i(\beta, t) &= S_i^{(2)}(\beta, t) / S_i^{(0)}(\beta, t) - E_i(\beta, t), \\
s_i^{(k)}(\beta, t) &= E\{S_i^{(k)}(\beta, t)\}, \\
e_i(\beta, t) &= s_i^{(1)}(\beta, t) / s_i^{(0)}(\beta, t), \\
v_i(\beta, t) &= s_i^{(2)}(\beta, t) / s_i^{(0)}(\beta, t) - e_i(\beta, t),
\end{aligned}
$$

for $i = 1, 2$, and $k = 0, 1, 2$, where for a column vector a, $a^{\otimes 0} = 1$, $a^{\otimes 1} = a$, and $a^{\otimes 2} = aa'$.

For simplicity of presentation, we assume $\{X_{ij}, T_{ij}, D_{ij}, Z_{ij}\}$, $(j = 1, \cdots, n_i)$ are independent and identically distributed, $P(T_{ij} \geq X_{ij}) > 0$, and $\{Z_{ij}\}$ is bounded. Left-truncated and right-censored survival data has been studied extensively. The more general conditions required to obtain large sample results for this type of data can be found in Woodroofe (1985), Lai and Ying (1991) and Andersen $et\ al$ (1993). Andersen $et\ al$ (1993) argued that the martingale central limit theory can be applied to the left-truncated data, so that the asymptotic results based on right censored data can be extended to the left-truncated and right censored data. Also we assume that two samples are independent. Let $n = n_1 + n_2$. Then, if $n_i/n \longrightarrow p_i > 0$, for $i = 1, 2$, $\hat{\beta}$ is an consistent estimate of β, and

$$\sqrt{n}(\hat{\beta} - \beta) \xrightarrow{\mathcal{D}} N(0, \Sigma^{-1}),$$

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where

$$\Sigma = \sum_{i=1}^{2} p_i \int_0^\infty v_i(\beta, t) s^{(0)}(\beta, t) \lambda_{i0}(t) dt,$$

which is assumed to be positive definite and can be consistently estimated by the observed information matrix

$$\hat{\Sigma} = \frac{1}{n} \sum_{i=1}^{2} \int_0^\infty V_i(\hat{\beta}, t) d\bar{N}_i(t).$$

To find the limiting distribution of

$$W(t; z_0) = \sqrt{n} \left\{ [\hat{F}_2(t; z_0) - \hat{F}_1(t; z_0)] - [F_2(t; z_0) - F_1(t; z_0)] \right\},$$

the delta-method can be used to show that this process behaves asymptotically like

$$W_1(t; z_0) = \sqrt{n} \{ F_1(t; z_0) [\hat{\Lambda}_1(t; z_0) - \Lambda_1(t; z_0)] - F_2(t; z_0) [\hat{\Lambda}_2(t; z_0) - \Lambda_2(t; z_0)] \}.$$

Let N_{ij} be the observed counting process and define the martingales

$$M_{ij}(t) = N_{ij}(t) - \int_0^t Y_{ij}(u) e^{\beta' Z_{ij}} \lambda_{i0}(u) du, \tag{1}$$

for $i = 1, 2$ and $j = 1, \cdots, n_i$. Let $\bar{M}_i = \sum_{j=1}^{n_i} M_{ij}$, Andersen and Gill (1982) showed that $W_1(t; z_0)$ is asymptotically equivalent to

$$\widetilde{W}(t; z_0) = \sqrt{n} F_1(t; z_0) \int_0^t \frac{e^{\beta' z_0} d\bar{M}_1(u)}{n_1 S_1^{(0)}(\beta, u)} - \sqrt{n} F_2(t; z_0) \int_0^t \frac{e^{\beta' z_0} d\bar{M}_2(u)}{n_2 S_2^{(0)}(\beta, u)}$$

$$+ \left(F_1(t; z_0) h_1(t; z_0) - F_2(t; z_0) h_2(t; z_0) \right)' \Sigma^{-1} \left\{ \frac{1}{\sqrt{n}} \sum_{i=1}^{2} \sum_{j=1}^{n_i} \int_0^\infty [Z_{ij} - E_i(\beta, u)] dM_{ij}(u) \right\}, \tag{2}$$

where $h_i(t; z_0) = \int_0^t e^{\beta' z_0} [z_0 - e_i(\beta, u)] \lambda_{i0}(u) du$, which can be estimated by

$$\hat{h}_i(t; z_0) = \int_0^t e^{\hat{\beta}' z_0(u)} [z_0 - E_i(\beta, u)] \frac{d\bar{N}_i(u)}{n_i S_i^{(0)}(\hat{\beta}, u)}.$$

By Rebolledo's martingale central limit theorem we can show that $\widetilde{W}(t; z_0)$ converges weekly to a zero mean Gaussian martingale on $[0, \tau]$, where $\tau < \inf\{t : EY_{ij}(t) = 0\}$, with covariate function

$$\xi(t, v; z_0) = \sum_{i=1}^{2} \frac{1}{p_i} F_i(t; z_0) F_i(v, z_0) \int_0^{t \wedge v} \frac{e^{2\beta' z_0} \lambda_{i0}(u) du}{s_i^{(0)}(\beta, u)}$$

$$+ \left(F_1(t; z_0) h_1(t; z_0) - F_2(t; z_0) h_2(t; z_0) \right)' \Sigma^{-1} \left(F_1(v; z_0) h_1(v; z_0) - F_2(v; z_0) h_2(v; z_0) \right).$$

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It follows that the variance of $W(t; z_0)$ can be consistently estimated by

$$\hat{\sigma}^2(t; z_0) = \sum_{i=1}^{2} \frac{n}{n_i^2} \hat{F}_i^2(t; z_0) \int_0^t \frac{e^{2\hat{\beta}' z_0} d\bar{N}_i(u)}{[S_i^{(0)}(\hat{\beta}, u)]^2}$$

$$+ \left(\hat{F}_1(t; z_0) \hat{h}_1(t; z_0) - \hat{F}_2(t; z_0) \hat{h}_2(t; z_0) \right)' \hat{\Sigma}^{-1} \left(\hat{F}_1(t; z_0) \hat{h}_1(t; z_0) - \hat{F}_2(t; z_0) \hat{h}_2(t; z_0) \right).$$

The limiting Gaussian process for $W(t; z_0)$ does not have independent increments, which makes the computation of the distribution of limiting functionals of $W(t; z_0)$ difficult. To approximate these limiting distributions we shall use a modification of a Monte Carlo technique proposed recently by Parzen et al (1997) and Lin et al (1994). First, note that the martingales $\{M_{ij}(u)\}$ in (1) have mean zero and variance $\{N_{ij}(u)\}$. By the results in Lin et al (1994), if one replaces $\{M_{ij}(u)\}$ with $\{G_{ij}N_{ij}(u)\}$, in (2), where G_{ij} are independent standard normal random variables, then the limiting distribution of $\widetilde{W}$, evaluated using the estimated regression coefficients and covariance matrix is the same as that of W. In particular, to construct the confidence band for $D(t; z_0) = F_2(t; z_0) - F_1(t; z_0)$, $t \in [t_1, t_2]$, we simulate N realizations of

$$\hat{B}(t; z_0) = \widehat{W}(t; z_0) / \hat{\sigma}(t; z_0),$$

with

$$\widehat{W}(t; z_0) = \sqrt{n} \hat{F}_1(t; z_0) \sum_{j=1}^{n_1} \int_0^t \frac{e^{\hat{\beta}' z_0} G_{1j} dN_{1j}(u)}{n_1 S_1^{(0)}(\hat{\beta}, u)} - \sqrt{n} \hat{F}_2(t; z_0) \sum_{j=1}^{n_2} \int_0^t \frac{e^{\hat{\beta}' z_0} G_{2j} dN_{2j}(u)}{n_2 S_2^{(0)}(\hat{\beta}, u)}$$

$$+ \left(\hat{F}_1(t; z_0) \hat{h}_1(t; z_0) - \hat{F}_2(t; z_0) \hat{h}_2(t; z_0) \right)' \hat{\Sigma}^{-1} \left\{ \frac{1}{\sqrt{n}} \sum_{i=1}^{2} \sum_{j=1}^{n_i} \int_0^{\infty} [Z_{ij} - E_i(\hat{\beta}_0, u)] G_{ij} dN_{ij}(u) \right\}. \quad (3)$$

A $(1 - \alpha) \times 100\%$ confidence band for $D(t; z_0)$ over the interval $[t_1, t_2]$ is given by

$$[\hat{F}_2(t; z_0) - \hat{F}_1(t; z_0)] \pm n^{-1/2} C_\alpha \hat{\sigma}(t; z_o),$$

where C_α is the $(1-\alpha) \times 100th$ percentile of the sample $\bar{B}^{(k)} = \text{Sup}_{t \in [t_1, t_2]} |\widehat{W}^{(k)}(t; z_0) / \hat{\sigma}(t; z_o)|$, for $k = 1, \cdots, N$, simulated from (3).

3. Example

To illustrate this approach we compare the survival probabilities of chronic phase chronic myelogenous leukemia (CML) patients treated with conventional chemotherapy against patients treated by an allogeneic bone marrow transplants. Patients treated with conventional chemotherapy were from a multicenter trial conducted by the German CML study group. Of the 196 patients in that study, 75 recieved primary treatment with interferon and 121 with hydroxyurea. Patients in this study arm were followed from the time of diagnosis to death or until the end of the study.

The transplant cohort included 548 patients receiving hydroxyurea or interferon pretreatment and a HLA-identical sibling bone marrow transplant (BMT). All patients were reported to the International Bone Marrow Transplant Registry (IBMTR). IBMTR is a voluntary working group of over 300 transplant centers worldwide that contribute data on their allogeneic bone marrow transplants to a Statistical Center° at the Medical College of Wisconsin. Patients in this arm were diagnosed between 1983 and 1991, and were between 15 and 55 years of age. For detailed patient characteristics see Gale *et al* (1998).

The IBMTR only records data on consecutive transplants from member institutions and does not provide data on patients who died while waiting for a transplant. Thus the transplant data is left truncated at the time of transplant. This left truncation can lead to a time-to-treatment bias (See Klein and Zhang (1996)) unless a proper adjustment is made to the risk set. Hence, at each time point, the risk set in the non-transplant cohort consists of all patients still under study while the risk set in the transplant cohort includes only those with a waiting time to transplant less than the current time point who are still under study.

For the CML data, the following covariates were associated with survival: sex (1–female, 0–male), spleen size (1–$\geq$ 10 cm, 0–otherwise), year of diagnosis (1–$\geq$ 1998, 0–otherwise), and age at diagnosis (1–$\geq$ 35 years, 0–otherwise). A test of interaction indicated that year of diagnosis had a different effect for the two treatments. We fit it separately for the two treatments. Also, the proportionality assumption did not hold for treatment effect, indicating that the relationship between treatment and outcome differed over time. We fit a Cox model stratified on treatment to the time from diagnosis to death. The regression coefficient estimates are given in Table 1.

Table 1. Regression coefficient estimates.

Variable	Coefficient Estimate	Standard Error
Sex	-0.434	0.139
Spleen size	0.461	0.146
Age	0.198	0.139
Year of diagnosis:		
Chemotherapy	0.120	0.216
Transplant	-0.553	0.182

When comparing two survival curves based on left-truncated data additional care is required in choosing the comparison interval, $[t_1, t_2]$. It is important to choose t_1 such that the risk sets at t_1 consists of a sufficient number of patients for both cohorts in order to make a stable comparison. We choose the comparison interval as $[6.4, 100.4]$ months since diagnosis. At 6.4 month, the sizes of the risk sets were 189 and 117 for non-transplant and transplant cohort respectively, and at 100.4 month both cohort had at least 10 patients still at risk.

We plot the predicted survival curves and the estimated differences for a particular set of covariates values. The critical value C_α was approximated based on 5,000 realizations of (3).

Figure 1a shows the estimated survival curves for a recently diagnosed ($\geq$ 1988) older ($\geq$ 35 years) male patient with large spleen size $\geq$ 10 cm. Figure 1b shows the estimated difference (BMT-Chemotherapy) between the two survival curves with a 95% pointwise confidence interval and 95% confidence band for such a patient. A similar plot for a patient diagnosed prior to 1988 with the same characteristics is given in Figure 2.

These confidence band plots indicated that the chemotherapy treatment has an early survival advantage due, perhaps, to the toxicity of the bone marrow transplant. There is a significant late survival advantage for transplant patient due to a lower relapse rate. Also for the recently treated cases (Figure 1) BMT had a survival advantage (95% confidence band is > 0) starting at 5.50 years after diagnosis. This is in contrast to patients treated prior to 1988 (Figure 2) where BMT started to show an advantage only after 8.29 years since diagnosis. This may be due to the improvement of bone marrow transplant techniques over the years.

In this example, there are 16 sets of possible covariates values. The time points since diagnosis where BMT starts to have a survival advantage are presented in Table 2. These time points ranged from 5.50 years to 8.29 years since diagnosis depending on the given patient characteristics. By contrast to the comparison of two Kaplan-Meier survival curves, this comparison of two predicted survival curves based on the Cox model provides more information to both the physicians and patients.

Table 2. Time points t_0 since diagnosis (DX) in years where BMT starts to have survival advantage.

Covariate Values				C_α	t_0
Sex	Spleen Size	Age	Year of DX		
M	< 10 cm	< 35	< 88	2.96	7.84
M	< 10 cm	< 35	$\geq$ 88	2.97	5.97
M	$\geq$ 10 cm	< 35	< 88	2.96	7.84
M	$\geq$ 10 cm	< 35	$\geq$ 88	2.99	5.88
M	< 10 cm	$\geq$ 35	< 88	2.99	7.84
M	< 10 cm	$\geq$ 35	$\geq$ 88	2.95	5.88
M	$\geq$ 10 cm	$\geq$ 35	< 88	2.96	8.29
M	$\geq$ 10 cm	$\geq$ 35	$\geq$ 88	2.94	5.50
F	< 10 cm	< 35	< 88	2.96	8.29
F	< 10 cm	< 35	$\geq$ 88	2.93	5.97
F	$\geq$ 10 cm	< 35	< 88	2.99	7.84
F	$\geq$ 10 cm	< 35	$\geq$ 88	2.98	6.24
F	< 10 cm	$\geq$ 35	< 88	2.92	7.84
F	< 10 cm	$\geq$ 35	$\geq$ 88	2.89	5.97
F	$\geq$ 10 cm	$\geq$ 35	< 88	2.90	7.84
F	$\geq$ 10 cm	$\geq$ 35	$\geq$ 88	2.92	5.88

4. Remarks

Plotting the confidence band for the difference of two predicted survival functions provides a valuable decision making tool for physicians and patients. The proposed simulation method is easy to program, and offers a flexible way to construct such confidence bands, particularly when the limiting distributions cannot be evaluated analytically. The proposed simulation method can be extended to compare the difference of two survival curves based on other models, such as Aalen's (1989) additive model or other more general models.

The estimated critical value, C_α, depends on the number of realizations N. It is important to know what is the appropriate N. In our example for an early diagnosed young (< 35 yr) male patient with small spleen size (< 10 cm), the estimated C'_αs were 3.01, 2.98, 2.97, 3.01, 2.97, and 3.01 for $N = 500, 1500, 3000, 5000, 8000$ and 10000, respectively. It appears that the estimate of C_α is resonably stable after only 500 replications.

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Figure 1(a). Predicted Probability of Survival for Recently Diagnosed,
Older, Male Patient with Large Spleen Size
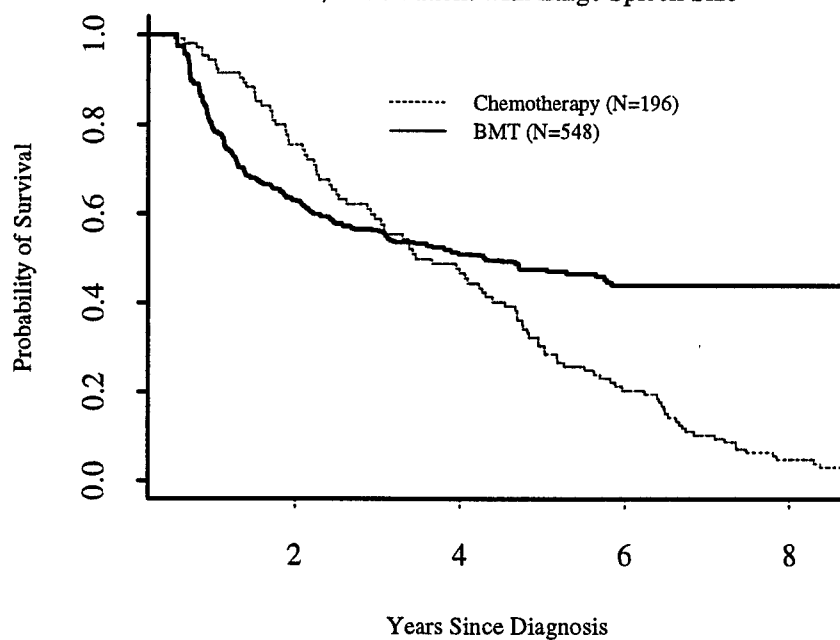
Figure 1(b). Difference of Survival Probabilities (BMT - Chemotherapy)
for Recently Diagnosed, Older, Male Patient with Large Spleen Size
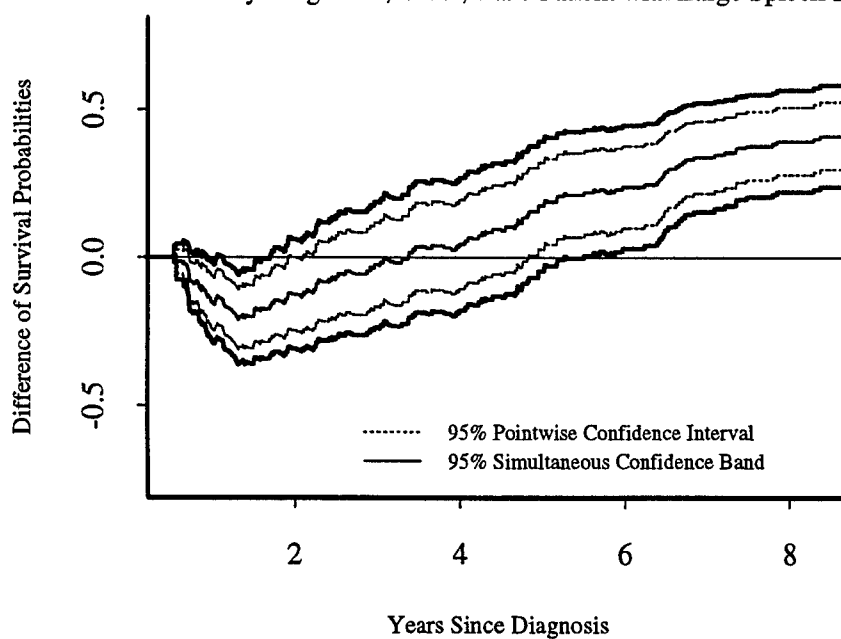
Figure 2(a). Predicted Probability of Survival for Early Diagnosed,
Older, Male Patient with Large Spleen Size

Chemotherapy (N=196)
BMT (N=548)

Probability of Survival

Years Since Diagnosis
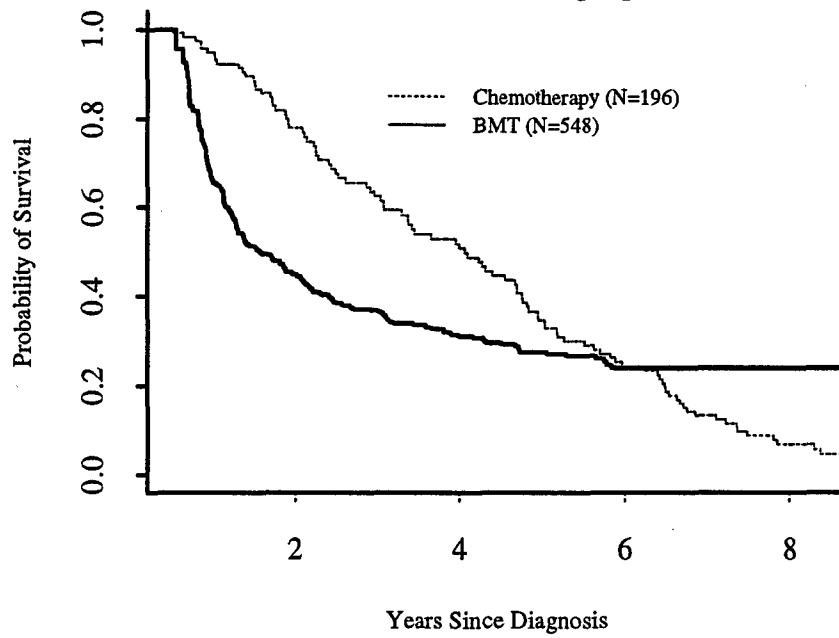
Figure 2(b). Difference of Survival Probabilities (BMT - Chemotherapy)
for Early Diagnosed, Older, Male Patient with Large Spleen Size
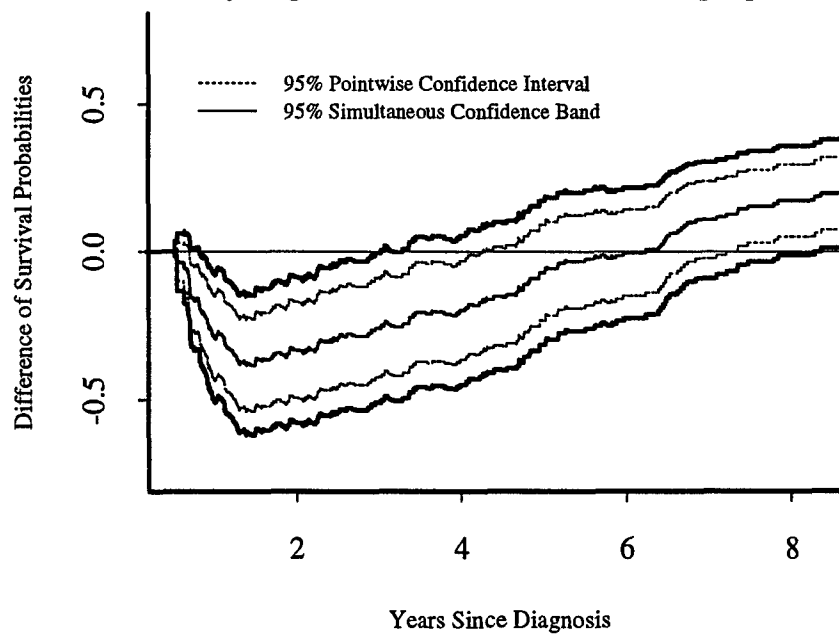
95% Pointwise Confidence Interval
95% Simultaneous Confidence Band

Difference of Survival Probabilities

Years Since Diagnosis

Modeling Multistate Survival
Illustrated In
Bone Marrow Transplantation

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MODELING MULTISTATE SURVIVAL ILLUSTRATED IN BONE MARROW TRANSPLANTATION

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1. INTRODUCTION

In many applications of survival analysis techniques the ultimate outcome of a patient's treatment depends on the occurrence and timing of some intermediate events. This is particularly true when studying the recovery process of a patient from a bone marrow transplant for leukemia. Here a patient can experience one of several terminal events, such as death in remission, reoccurrence of their leukemia or simply death. As the patient recovers from their transplant a number of intermediate events may occur that have an influence on their eventual prognosis. Examples of such intermediate events are the return of the patient's platelets to a "normal" level, the development of various types of infections, the occurrence of acute or chronic graft-versus-host disease, etc.

A natural way to model complex experiments such as this is by using a multistate model. Andersen et al (1991) (See also Andersen et al 1993) has studied such models using a finite state Markov process model where the hazard rates for each possible transition in the multistate model are modeled by a separate Cox (1972) proportional hazards model. Here each of the transition probabilities is estimated using a (left truncated) Cox model. In a multistate model with two intermediate events and two terminal events this entails fitting 12 separate Cox models.

Recently, Klein et al (1993) have suggested an alternative approach to multistate modeling. They suggest fitting a Cox model to each of the events with time dependent covariates used to model the timing of the intermediate events that precede the event of interest. In a multistate model with two intermediate events and two terminal events this entails fitting 4 separate Cox models. This model is discussed in Section 3.

The Klein and Andersen approach are two extremes of how one can model multistate survival. In this report we shall examine how one may model multistate survival experiments where some of the transition rates are assumed to be proportional to others. This general model is discussed in Section 4.

Once the transition rates are modeled it is necessary to synthesize these rates to provide predictions of the patient's eventual prognosis. The patient's prognosis is a dynamic entity that depends on their history at a given point in time. The models we fit allow us to estimate a series of

predictive probabilities based on potential patient histories which may be observed at some time t. These patient histories include the information known on the patient at entry to the study (the fixed-time covariates) and the knowledge of when the intermediate events have occurred.

Recently, Arjas and Eerola (1994) (cf. Eerola (1993)) have described a framework of "predictive causality" for longitudinal studies that can be used to illustrate how the timing of the occurrences of the time dependent covariates in a patient's recovery process changes the prediction of his or her final prognosis. For a given patient, let $(T,X)=\{(T_m,X_m); m \geq 1\}$ denote the ordered times, $0 \leq T_1 \leq T_2 \leq ...$, at which events occur during a patient's recovery from transplantation, with description, X_m, of what has happened to the patient at time T_m. In the bone marrow transplantation recovery process X_m may denote return of the platelets to normal levels, the development of acute GVHD, or the occurrence of relapse, or death. A patient history, H_t, at some time t post-transplantation consists of all the pre-transplantation information available on the patient (the fixed-time covariates) and the set of marked points, $\{(T_m,X_m); T_m \leq t\}$, reflecting what has happened to the patient up to this point in time. We consider the prediction that some event, W, such as relapse, occurs in time interval, E ($W \in E$), for example within two years post-transplantation. The predicted probability that $W \in E$ should depend on the patient's history at the time t at which this prediction is made. We define a prediction process by $\mu_t(E)=P[W \in E|H_t]$

The prediction process allows us to examine the effect of time dependent (and fixed-time) covariates on the predicted prognosis of a given patient in three ways. First, we can fix the time t and the history, H, for a patient up to time t and see how the predicted probability of W being in E changes as the prediction interval E varies. In the bone marrow transplantation example this will allow us to estimate how the probability of relapse within τ years post-transplantation, changes as τ varies for a patient with a given history at time t. That is, given a particular history at a given time for a patient we can provide a prognosis for this patient at times in the future. Second, we can fix a potential history, H, for a patient and the prediction interval, E, and see how the $\mu_t(E)$ changes as t increases. For example, for a patient with a given history of development of acute GVHD or platelet recovery, this will give insight into how more and more of a patient history allows us to refine our prediction of the chance that he or she would relapse within the first two years post-transplantation, say. Arjas and Eerola call this the learning effect. Finally, we can fix the prediction interval, E, and the time at which we observe the patient history, t, and look at the prediction process for patients with different histories. This allows us to study directly the effect of the timing of the intermediate endpoints on the prognosis of future patients. In the bone marrow transplantation recovery process this may suggest to the physician that, if certain events have not occurred by a given time, some additional therapy should be given, based on this model.

The example that is used throughout this paper is from a multicenter bone marrow transplantation study of patients given an HLA identical sibling transplants, conducted between

1985 and 1990, for patients with acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia reported to the International Bone Marrow Transplant Registry. The data set consists of 1823 patients with observation times ranging from 10 days to 2236 days. 957 patients were alive and disease free at their last observation time, 442 died in remission and 424 patients were observed to relapse. In Section 2 a multistate model for this data is presented and in Section 5 we shall present some empirical estimates of the predicted probabilities.

2 BONE MARROW TRANSPLANTATION

Bone marrow transplantation is a standard treatment for acute leukemia. Recovery following bone marrow transplantation is a complex process. Prognosis for recovery may depend on risk factors known at the time of transplantation, such as patient's or donor's age and sex, the stage of initial disease, the time from diagnosis to transplantation, and so on. The final prognosis may change as the patient's post-transplantation history develops with the occurrence of events during the recovery process, such as the development of acute or chronic graft-versus-host disease (GVHD), the return of the platelet count to normal levels, the return of granulocytes to normal levels, or the development of infections. Transplantation can be considered a failure when a patient's leukemia returns (relapse) or when he or she dies while in remission (treatment-related death). Of interest is how the probabilities of relapse (denoted by R) and treatment-related death (denoted by D), as well as leukemia-free survival (the probability of being alive and in remission), depend on the pre-transplantation (fixed-time covariates) and post-transplantation (time dependent covariates) patient history.

Figure 1 shows a simplified diagram of a patient's recovery process based on two intermediate events which may occur in the recovery process. These intermediate events are the development of acute GVHD which typically occurs within the first 100 days following transplantation (denoted by an A), and the recovery of the platelet count to a self-sustaining level $\geq$ 40 x 10^9/L (called platelet recovery in the sequel and denoted by a P). Immediately following transplantation, patients have depressed platelet counts and are free of acute GVHD. At some point in time they may develop acute GVHD or have their platelets recover, at which time their prognosis (probabilities of treatment-related death or relapse at some future time) may change. These events may occur in any order or a patient may die or relapse without any of these events occurring. Patients may then experience the other event, which again modifies their prognosis, or they may die or relapse.
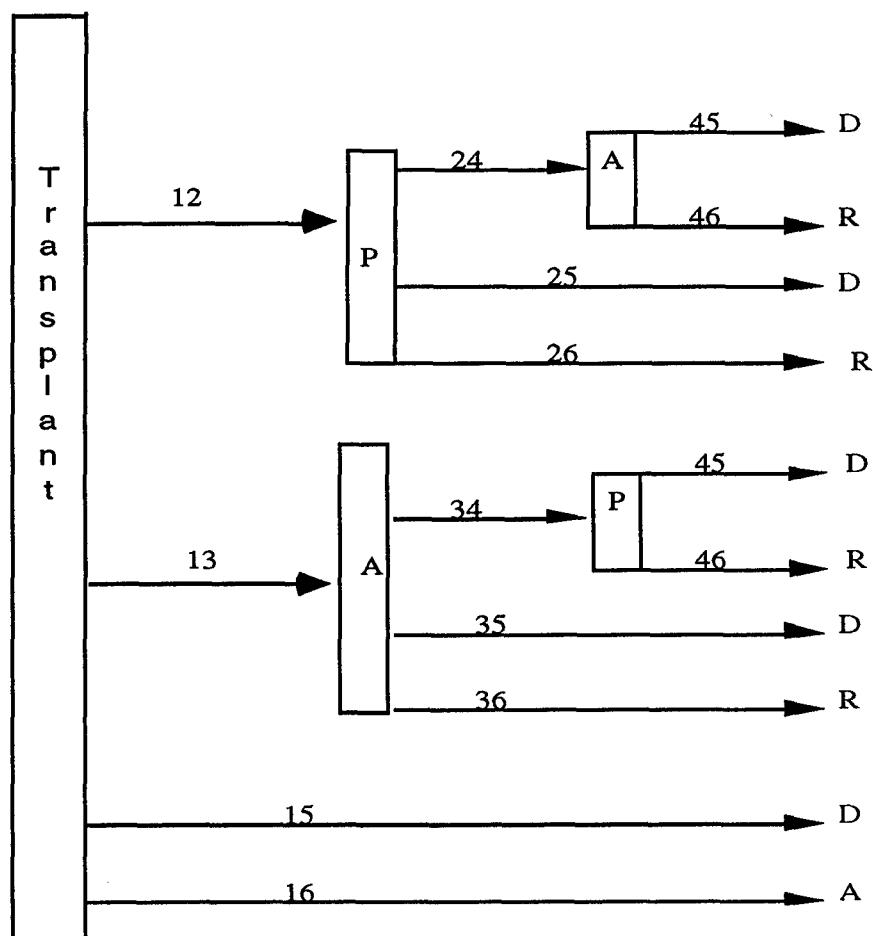
FIGURE 1

Multistate Model For Bone Marrow Transplant Recovery

Figure 1 shows that there are 12 possible transitions that can occur in this multistate model. There are six possible states in which a patient may be in at any given time, t. These states are:

1-$\{T_P \geq t, T_A \geq t, T_D \geq t, T_R \geq t\}$ (Alive disease free without having GVHD or having had platelets recovered)

2-$\{T_P < t, T_A \geq t, T_D \geq t, T_R \geq t\}$ (Alive disease free without having GVHD with platelets recovered)

3-$\{T_P \geq t, T_A < t, T_D \geq t, T_R \geq t\}$ (Alive disease free without platelets recovered having experienced GVHD)

4-$\{T_P < t, T_A < t, T_D \geq t, T_R \geq t\}$ (Alive disease free with platelets recovered having experienced GVHD)

5 - $\{T_D < t, T_R \geq t\}$ (Dead prior to relapse)

6- $\{T_D \leq t, T_R < t\}$ (Relapsed)

3. PROPORTIONAL HAZARDS MODEL

In this section we shall present a basic model for multistate survival studies based on a series of Cox regression analysis using time dependent covariates. To model survival we assume that an individual is at risk having any one of the events in some set e. This set consists of both the intermediate events which may affect a patient's eventual prognosis and the terminal events. In the bone marrow transplant example the set e is {A, P, R, D}, where A is the event GVHD has occurred, P is the event the platelets have recovered, R is the event relapsed and D is the event died.

From the events in the set e we can define a set of states s = {1,2,...,p}. Each element of s tells us which final event has occurred or what combination of intermediate events has occurred. In the transplant example there are six states listed in the previous section.

For a given model only certain transitions are possible. We let t be the set of possible transitions. In the transplant example t has twelve elements as shown in Figure 1. That is t ={12, 13, 15, 16, 24, 25, 26, 34, 25, 26, 45, 46}. For any event X ∈ e we define t(X) as the set of transitions into event X that are possible. In our example t(P) ={12, 34}, t(A) ={13, 23}, t(D) ={15, 25, 35, 45}, and t(R) ={16, 26, 36, 46}.

For any event, X, in e we define the ancestor set a(X) as the set of intermediate events that may happen prior to the occurrence of the event X. In our example we have a(P)= {A}, a(A)= {P} and a(R)= a(D) = {A, P}.

To model the transitions rates for this model we shall use a proportional hazards regression model. For each event, X, in e we fit a proportional hazards regression model which includes the fixed time covariates specific to the event as well a time dependent covariate for each of the events in the ancestor set of X. If we let Z_F be the vector of fixed time covariates that have an influence on any event in e and let β_{FX} be a vector of risk coefficients for these covariates for the event X. Note that if a fixed covariate has no effect on the timing of event X then the risk coefficient for that factor is set to 0. The model for the hazard rate of the time to event X is given by

$$\lambda(t \mid Z_F) = \lambda_{0X}(t) \exp\left\{ \beta_{FX} Z_F + \sum_{x' \in a(X)} \beta_{x'x} I[T_{x'} < t] \right\}. \tag{3.1}$$

Here I[] is the indicator function and $\beta_{x'x}$ is the risk coefficient for the effect of the occurrence of event X' on the time to event X. The baseline hazard rate, $\lambda_{0X}(t)$, can be different for distinct levels of some fixed covariates although for simplicity we shall consider the unstratified case in the sequel. The parameters in (4.1) can be estimated from any standard Cox regression package.

Using the model (4.1) the hazard rate for any of the transitions in the set t can be modeled. Specifying a transition determines X and the values to be assigned to the indicators $I[T_X < t]$ for any intermediate event. For example,

$$\lambda_{15}(t \mid Z_F) = \lambda_{0D}(t) \exp\{\beta_{FD}Z_F\}$$

$$\lambda_{25}(t \mid Z_F) = \lambda_{0D}(t) \exp\{\beta_{FD}Z_F + \beta_{PD}\}$$

$$\lambda_{35}(t \mid Z_F) = \lambda_{0D}(t) \exp\{\beta_{FD}Z_F + \beta_{AD}\}$$

and

$$\lambda_{45}(t \mid Z_F) = \lambda_{0D}(t) \exp\{\beta_{FD}Z_F + \beta_{PD} + \beta_{AD}\}.$$

For any transition, ij, we define the cumulative transition rate as

$$\Lambda_{ij}(t \mid Z_F) = \int_0^t \lambda_{ij}(u \mid Z_F) du, \quad i \neq j, \ i,j \in t$$

$$\Lambda_{ij}(t \mid Z_F) = 0 \text{ if } i \neq j, \ i,j \notin t, \text{ and}$$

$$\Lambda_{ii}(t \mid Z_F) = -\sum_{j \in s} \Lambda_{ij}(u \mid Z_F), \quad i \in s.$$

Since $\Lambda_{ij}(t \mid Z_F)$ is absolutely continuous for any $i,j, \in s$ it follows that the matrix $\Lambda = (\Lambda_{ij})_{pxp}$ is the transition intensity of a Markov process with state space $s = \{1,...,p\}$ (See Andersen et al pp 92-93). The transition probability matrix of this Markov process is given by

$$P[s,t \mid Z_F] = \prod_{s < u \leq t}[I + d\Lambda(u \mid Z_F)], \tag{3.2}$$

where Π is the product-integral (cf. Gill and Johansen (1990) for details on the matrix product integral) and I is the pxp identity matrix. This transition probability matrix serves as the basis for making an inference about a patient's eventual prognosis given their current history.

To estimate the transition probability matrix the required Cox models are fit and the estimators of β are obtained. Breslow's estimator of the baseline hazard (Breslow 1972) rates are then computed and substituted into (4.2). For the bone marrow transplant example this yields the following estimators of the predicted probabilities (Here we shall ignore the dependence on Z_F for notational convenience)

$$\hat{P}_{ii}(s,t) = \prod_{s<u\le t} \{1 - \sum_{j:i<j}\Delta\hat{\Lambda}_{ij}(u)\}, \ i=1, 2, 3, 4;$$

$$\hat{P}_{ij}(s,t) = \sum_{s<u\le t}\hat{P}_{ii}(s,u-)\,\hat{P}_{jj}(u,t)\,\Delta\hat{\Lambda}_{ij}(u) \ , \ ij=12,13,24, 34,45,46;$$

$$\hat{P}_{ij}(s,t) = \sum_{s<u\le t}\hat{P}_{ii}(s,u-)[\ \Delta\hat{\Lambda}_{ij}(u)+\hat{P}_{4j}(u,t)\Delta\hat{\Lambda}_{i4}(u)] \ , \ ij=25,26, 35, 36;$$

and

$$\hat{P}_{1j}(s,t) = \sum_{s<u\le t}\hat{P}_{11}(s,u-)[\ \Delta\hat{\Lambda}_{1j}(u)+\hat{P}_{2j}(u,t)\Delta\hat{\Lambda}_{12}(u)+\hat{P}_{3j}(u,t)\Delta\hat{\Lambda}_{13}(u)], \ j=4,5,6.$$

The asymptotic distribution of $\mathbf{P}[s,t\mid \mathbf{Z_F}]$ can be obtained by basic counting process techniques. Details are found in Qian(1995). The basic result is as follows (Here for ease of exposition we have suppressed the dependence on the fixed covariates, $\mathbf{Z_F}$) :

Theorem 1 Under suitable regularity conditions each of the elements of the random matrix $\sqrt{n}\{\hat{\mathbf{P}}[s,t\mid \mathbf{Z_F}] - \mathbf{P}[s,t\mid \mathbf{Z_F}]\}$ converges weakly to a zero-mean Gaussian martingale with covariance function given by

$$Cov(\sqrt{n}(\hat{P}_{ij}(s,t), \hat{P}_{km}(s,t)) = \sum_{X\in e}\left\{\int_s^t \frac{F_{ij,X}(s,u,t)\ F_{km,X}(s,u,t)}{s_x^{(0)}(\beta_X,u)}d\Lambda_{0X}(u) + G'_{ij,X}\Sigma_X^{-1}G_{km,X}\right\},$$

where

$$F_{ij,X} = \sum_{\substack{gh\in t(X)\\ i\le g<h\le j}} D_{ighj,X}(s,u,t); \ ij\in s$$

$$G_{ij,X}(s,t)=\int_s^t \sum_{\substack{gh\in t(X)\\ i\le g<h\le j}} \{D_{ighj,X}(s,u,t)[\mathbf{Z_{gl}} - e_X(\beta_x,u)]d\Lambda_{0x}(u))\}; \ ij\in s$$

$$D_{ighj,X}(s,u,t) = \exp\{\beta_X\mathbf{Z_{gh}}\}\,P_{ig}(s,u-)\,[P_{hj}(u,t) - P_{gj}(u,t)] \ ij, gh\in s.$$

$$s_x^{(0)}(\beta_X,u) = \sum_{l=1}^n \exp\{\beta_X Z_{Xl}(u)\}Y_{Xl}(t),$$

$$e_X(\beta_X, u) = \frac{\sum_{l=1}^{n} Z_{Xl}(u) \exp\{\beta_X Z_{Xl}(u)\} Y_{Xl}(t)}{s_x^{(0)}(\beta_X, u)} ; \text{ and}$$

Σ_X is the covariance matrix of the estimates of β_X.

Here Z_{jk} is the union of the set of fixed covariates with a set of indicator covariates that tell us that an individual is in state j at time t. $Y_{Xl}(t)$ is the indicator that individual l is at risk for event X at time t, and $Z_{Xl}(t)$ is the covariate vector for event X for individual l at time t.

Estimators of the variability of the predicted probabilities are obtained by substituting the appropriate estimator into the covariance in Theorem 1. In particular we have that the variance of $\hat{P}_{ij}(s,t)$ is estimated consistently by

$$\sum_{X \in e} \left[\int_s^t [\frac{\hat{F}_{ij,X}(s,u,t)}{S_x^{(0)}(\beta_X, u)}]^2 dN_X(u) + \hat{G}_{ij,X}^{'} i^{-1}(\hat{\beta_X}) \hat{G}_{ij,X} \right], \tag{3.3}$$

where $dN_x(t)$ is the number of type X events occurring at time t and i_X is the observed information matrix for the regression estimates for event X.

4. Child-Event Models

The model constructed in Section 3 assumes that for any event X in e the hazard rates of any two X transitions ij, km $\in$ t(X) are proportional. This is a testable hypothesis that may fail to be true in some circumstances. In this section we shall look at models that relax this assumption.

To relax this proportionality assumption we consider models with time dependent stratification. Suppose we can divide the ancestor set a(X) into two disjoint sets $a_s(X)$ and $a_c(X)$. Here $a_s(X)$ is the set of ancestors of X for which a time dependent stratification will be used and $a_c(X)$ is the set of ancestors for which the proportional hazards modeling will be used. Let m(X) = 2 to the power the number of elements in $a_s(X)$. Here m(X) is the total number of distinct baseline hazard rates to be fit in the model. Number the m(X) baseline hazard rates from (0, ...,0) to (1,....,1). At an event time T_X we shall call an event a type X_hth event if h=(I[$T_{x'}$<t], X'$\in a_s(X)$). Thus we have created m(X) "child-events", X_h, from each parent-event X. The X_h transition set is naturally t(X_h) = {ij$\in$ t(X): {h=(I[$T_{x'}$<t], X'$\in a_s(X)$)}} as determined by state i}.

For each child event a distinct baseline hazard rate is assumed so that

$$\lambda_{X_h}(t| Z_F) = \lambda_{0X_h}(t) \exp\{\beta_{FX} Z_F + \sum_{X' \in a_c(X)} \beta_{X'X} I\{T_{X'} <t\}\}$$

and the hazard rate for each X_h transition is

$$\lambda_{ij}(t) = \lambda_{0X_h}(t) \exp\{\beta_X Z_{ij})\}.$$

Here Z_{ij} consists of the fixed covariates and a vector of 0 and 1's with a 1 in the correct position for any event in $a_c(X)$ which must have occurred prior to time t to be in state i.

Estimates of $\Lambda_{0X_h}(t)$ and the β's can be obtained from standard Cox regression packages. As opposed to the proportional hazards model, in this analysis there may be some time dependent stratification so that left truncated regression models must be employed. Once the parameter estimates are obtained and an estimate for $\Lambda_{ij}(t)$ is obtained then these can be used in (3.2) to obtain estimates of the predicted probabilities.

To illustrate this approach consider the bone marrow transplantation example. One possible time dependent stratification is to fit different baseline rates for the death event for individuals whose platelets have or have not recovered. Consider the parent event D whose ancestors are the events P and A. The set a(D) is divided into the sets $a_c(D)= \{A\}$ and $a_s(D)=\{P\}$. Two child events, D_1 and D_2 are defined by $\{T_P \geq T_D\}$ and $\{T_P < T_D\}$. Here D_1 is the event death without platelets being recovered and D_2 the event death with platelets recovered. Two proportional hazards models are fit for to the death event. The first model is $\lambda_{D_1}(t \mid Z_F)= \lambda_{0D_1}(t) \exp\{\beta_{FX} Z_F + \beta_{AD}I[T_A \leq t]\}$. Individuals are censored for λ_{0D_1} when their platelets recover. For the second model we have $\lambda_{0D_2}(t) \exp\{\beta_{FX} Z_F + \beta_{AD}I[T_A \leq t]\}$. Here the analysis for λ_{0D_2} is based on a left truncated Cox regression model with individuals entering the risk set at the time at which their platelets recover. The four transition rates to the state D are

$$\lambda_{15}(t \mid Z_F) = \lambda_{0D_1}(t) \exp\{\beta_{FX} Z_F\},$$
$$\lambda_{25}(t \mid Z_F) = \lambda_{0D_2}(t) \exp\{\beta_{FX} Z_F\},$$
$$\lambda_{35}(t \mid Z_F) = \lambda_{0D_1}(t) \exp\{\beta_{FX} Z_F + \beta_{AD}\}; \text{ and}$$
$$\lambda_{45}(t \mid Z_F) = \lambda_{0D_2}(t) \exp\{\beta_{FX} Z_F + \beta_{AD}\}.$$

If in addition to stratifying on the recovery time for the platelets we also stratify for D on the occurrence of acute GVHD we have $a_s(D)=\{P,A\}$ and $a_c(D)$ is the empty set. Now there are four child events for D corresponding $h = (0,0), (1,0), (0,1)$ and $(1,1)$. These correspond to the states $\{T_P >T_D, T_A>T_D\}$, $\{T_P \leq T_D, T_A>T_D\}$, $\{T_P >T_D, T_A \leq T_D\}$ and $\{T_P \leq T_D, T_A \leq T_D\}$, respectively. The models for the transitions into state D contain distinct baseline hazard rates for each of these states, and there are no time dependent covariates in the model.

The asymptotic properties of the estimated prediction probabilities are similar to those in theorem one with the simple change of the summations over $X \in e$ being changed to double sums over both $X \in e$ and $h=1,...,m(X)$. For example, the estimated variance of the predicted probability of a type ij transition in the time period (s,t] is

$$\hat{V}(\hat{P}_{ij}(s,t)) = \sum_{x \in e} \sum_{h=1}^{m(X)} \left[\int_s^t [\frac{\hat{F}_{ij,X}(s,u,t)}{S_{X_h}(0)(\beta_X,u)}]^2 dN_{X_h}(u) + \hat{G}'_{ij,X_h} i^{-1}(\hat{\beta}_X)\hat{G}_{ij,X_h} \right].$$

In the model presented above the coefficient vector, β_X, is the same for all child events, X_h. This assumption can be relaxed as well by allowing each child event to have its own β. This involves fitting separate Cox models for each child event. The estimation process follows as above. Here an estimate of the asymptotic variance of $\hat{P}_{ij}(s,t)$ is

$$\hat{V}(\hat{P}_{ij}(s,t)) = \sum_{x \in e} \sum_{h=1}^{m(X)} \left[\int_s^t [\frac{\hat{F}_{ij,X_h}(s,u,t)}{S_{X_h}(0)(\beta_{X_h},u)}]^2 dN_{X_h}(u) + \hat{G}'_{ij,X_h} i^{-1}(\hat{\beta}_{X_h})\hat{G}_{ij,X_h} \right].$$

The extreme case of this model is where all events are divided to their fullest (i.e. each child event corresponds to one and only one transition) and each transition has its own β. This is the usual model for multi-state processes introduced by Andersen et al (1991) (Cf. Andersen et al (1993) Section VII.2).

5. BONE MARROW TRANSPLANT EXAMPLE

To illustrate these calculations we shall fit the multistate proportional hazards model to the data from the International Bone Marrow Transplant Registry. As shown in figure 1 we have a model with two intermediate events, platelet recovery (P) and acute GVHD (A) and two terminal events, death in remission (D) and relapse (R). There were 1823 patients in the data set.

After a careful examination of the effects of various fixed time covariates on the four events we found that the most important covariates were the patients Karnofsky score at transplant, their waiting time from diagnosis to transplant and their age. In testing for proportional hazards for each of these covariates using a time dependent covariate approach (See Klein and Moeschberger (1996)) we found that the relapse hazards were not proportional at different ages. In the analysis reported below we have decided to stratify all the analysis on age (two strata age ≤ 20 or age >20). The other two risk factors were discretized as Karnofsky Score ≤ 80 versus Karnofsky score ≥ 90, and time from diagnosis to transplant ≤ 10 weeks versus >10 weeks.

To apply the proportional hazards model we fit four Cox models to the data, one for each of the four endpoints. For each event, X, we include a time dependent covariate for each event in a(X). The results are found in Table 1.

Table 1

Estimated Risk Coefficients And Standard Errors For The Proportional Hazards Model

Covariate	Platelet Recovery	Acute GVHD	Death in Remission	Relapse
Karnofsky Score ≤80	-.333 (.075)	.208 (.109) *	.359 (.108)	.414 (.119)
Waiting Time >10 Weeks	-.062 (.060) *	.014 (.099) *	.411 (.099)	.351 (.102)
Platelet Recovered		-.347 (.166)	-1.405 (.116)	-.322 (.126)
Acute GVHD	-0.433 (.074)		1.172 (.097)	-.283 (.130)

* Not significant at 5% level

Here we see that patients with a low Karnofsky score tend to take longer to have their platelets recover and are more likely to die or relapse. Patients with a long waiting time to transplant also have an increased risk of relapse and death.

Examining the two time dependent covariates we see that when a patient's platelets recover their risks of GVHD, death and relapse are decreased. When a patient develops GVHD their risk of relapse is decreased but their risk of death is increased. This decease in relapse risk is the well-known graft-versus-leukemia effect of GVHD.

To examine the fit of the proportional hazards model we also fit the Andersen model with distinct baseline hazard rate (stratified on age) and different covariate values for each transition. Here a standard Cox model is used for transitions 12, 13, 15, 16 and left truncated Cox models are used for all other transitions. The results are in Table 2.

Table 2
Estimated Risk Coefficients And Standard Errors From Fitting The Andersen Model

Transition	Karnofsky Score ≤80	Waiting Time >10 Weeks
1->2	-.319 (.083)	-.065 (.065)*
1->3	.251 (.115)	-.013 (.106)
1->5	.422 (.185)	.760 (.170)
1->6	.609 (.251)	.518 (.239)
2->4	-.098 (.364)*	.189 (.288)*
2->5	.959 (.254)	.031 (.267)*
2->6	.332 (.157)	.246 (.127)
3->4	-.334 (.173)	-.040 (.146)
3->5	.142 (.190)*	.330 (.180)*
3->6	1.063 (.454)	.445 (.434)*
4->5	.235 (.273)*	.297 (.233)*
4->6	.133 (.372)*	.474 (.297)*

* Not significant at 5% level

To examine the fit of the simpler proportional hazards we plot in Figure 1 the logs of the baseline hazards estimated from the Andersen model for each of the transitions. If the proportional hazards model holds true then we should have parallel curves for each transition into one of the four events. A cursory look at these figures does not suggest any marked departure from proportionality.

We shall use the proportional hazards multistate model to examine how a patient's prognosis at one year after transplant depends on their history in the first few weeks of their recovery process. We first estimate the probability of dying in remission in the first year given the patient's history at s weeks following transplant for each of the four possible states a patient may be in at s weeks. This estimated probability is given by $\hat{P}_{i5}[7s,365]$. Figure 2 shows the estimates under the proportional model for an individual who is under 20 years of age with a Karnofsky score of 90 or more and a waiting time to transplant of less than 10 weeks. Other values of the fixed covariates would give slightly different pictures. Here a patient is initially in the state 1 and we see that when their platelets recover their risk of death drops. The development of GVHD at any point in time elevates the chance of death. This probability is particularly high if the platelets have yet to recover. Figure 3 gives the one year probability of relapsing for each of the four states. Here again a patient is initially in state 1 and has a relatively high likelihood of relapsing. When graft-versus-host disease occurs this probability drops.

Figure 4 gives the leukemia free survival probabilities for the first year given a patient's history at s weeks. This is the probability of being alive and disease free at the end of the first year after transplant. This probability is given by 1- $\{P_{i5}[7s,365]+ P_{i6}[7s,365]\}$. The curves naturally increase as a patient survives disease free for a longer time. We see that once a patient has their platelets recover their prognosis is much better. The occurrence of GVHD without the platelets being recovered leads to the least favorable prognosis.

Figure 5 shows 95% confidence intervals and point estimates for the leukemia free survival at one year for each possible history a patient may have at s weeks. For comparison the proportional hazards and Andersen models are presented. Here we note that the confidence intervals based on the proportional hazards model are shorter. This is to be expected since this model has fewer parameters to estimate.

6 DISCUSSION

In our example we have presented estimates of predicted probabilities for some basic outcomes in bone marrow transplantation for a patient with a given history at some point in their recovery process. Similar plots can be used to examine how different values of the fixed time covariates affect the predicted patient prognosis.

We have chosen here to fix the time, t, to which the prediction is made at one year and to see how changes in the history affect the estimated probabilities. We could have fixed the time at which the history was measured and draw a curve for a range of times. These curves would be predicted survival curves given a patient's history at some time. An example of this approach can be found in Klein et al (1993).

The models presented here can also be used to provide some insight into how changing the rate or the timing of intermediate events effect a patient's eventual prognosis. For example, if some therapy was developed to increase the rate at which platelets recover this hypothetical therapy could be compared to existing therapy by modifying the baseline platelet recovery hazard rate and examining the predicted probabilities of death and relapse. This approach can also be used to examine how changing the rate at which one competing risk occurs affects the occurrence of another competing risk. For example, if the treatment mortality rate where cut in half how does this effect the predicted probability of relapse? This approach is more reasonable than existing methods for analyzing competing risks where one postulates a world in which one of the competing risks can not occur.

The basis of all the models presented here is a sound preliminary analysis of the data using proportional hazards regression models. This analysis involves not only finding important prognostic factors, but also involves checking of the proportionality assumptions of the models to determine the number of child events.

ACKNOWLEDGMENTS

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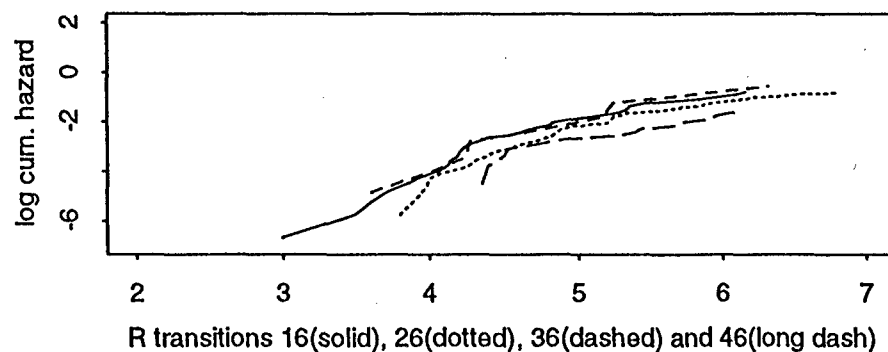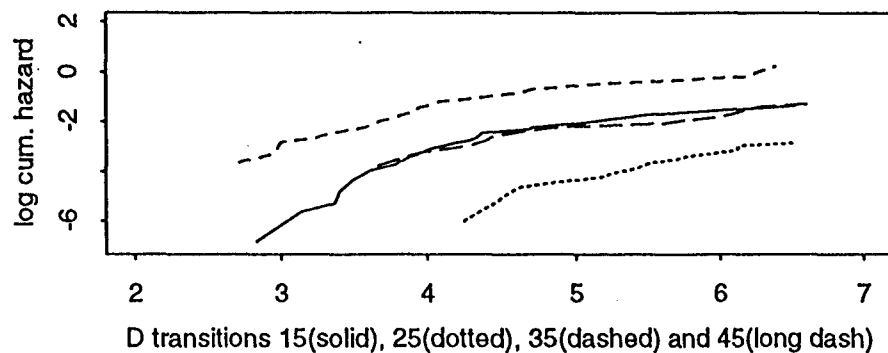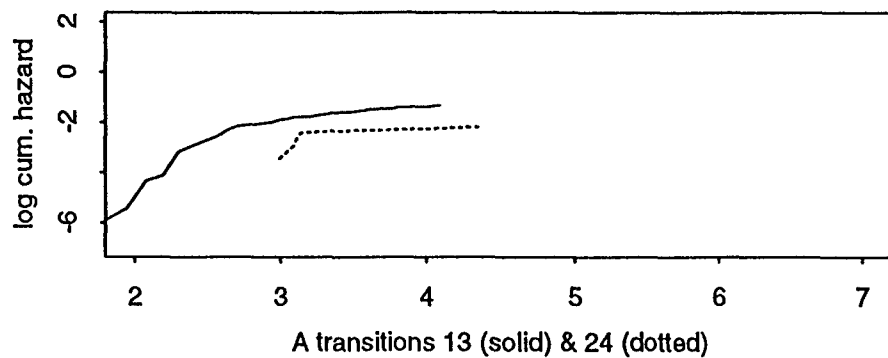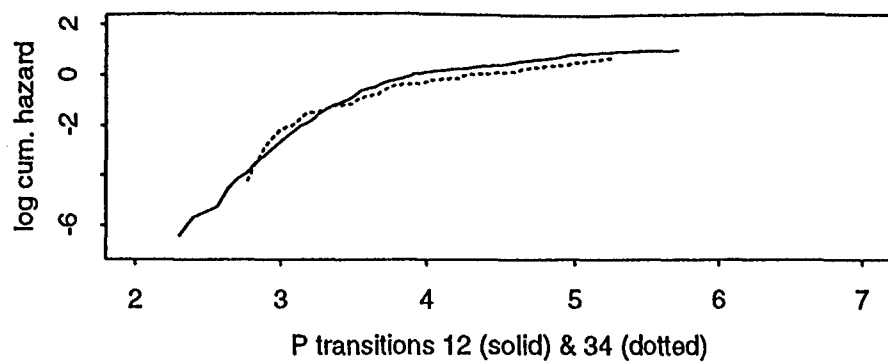
Figure 2: Baseline Log Cumulative Hazards From the Andersen Model
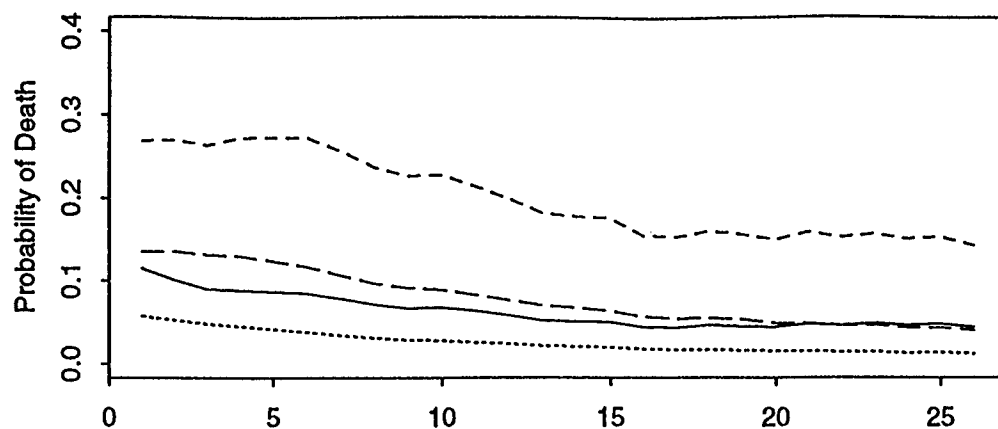
Figure 3: The One Year Death Probabilities Given State = i (*)
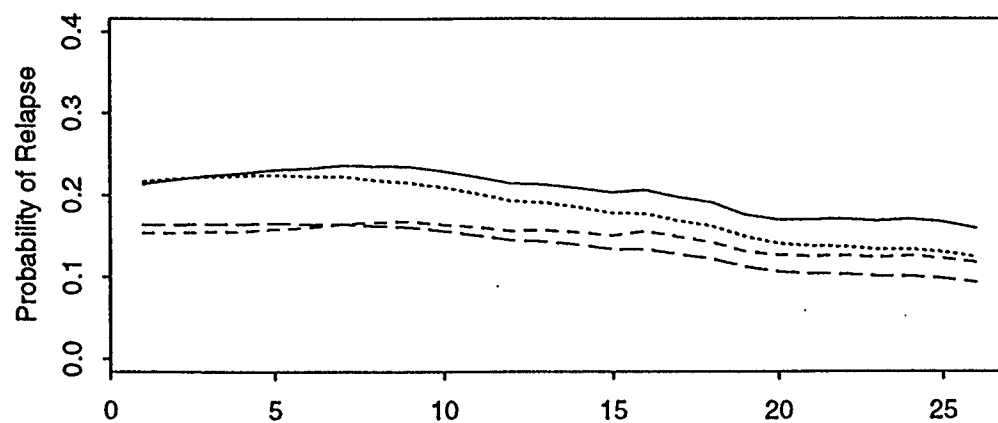
Figure 4: The One Year Relapse Probabilities Given State = i (*)
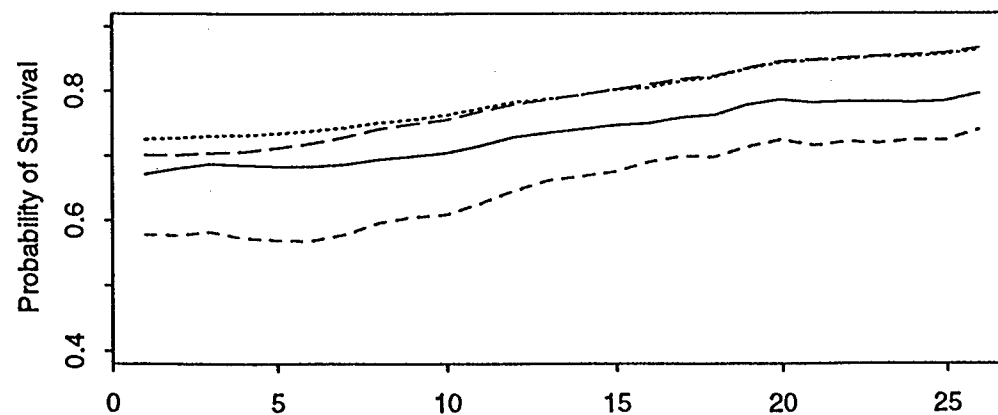
Figure 5: The One Year Leukemia-Free Survival Probabilities Given State = i (*)

(*) The x axes are time in weeks.
The four curves correspond to the states in the following order:
solid : i=1, dotted : i=2, dashed : i=3, and long dash : i=4.
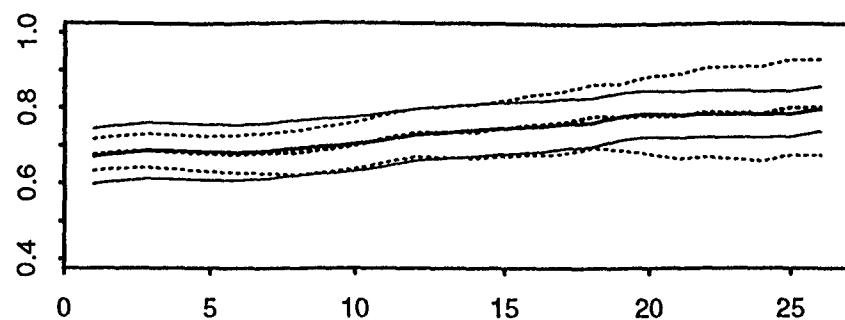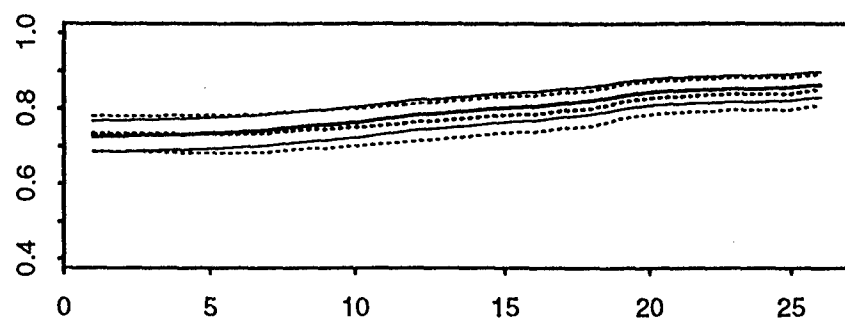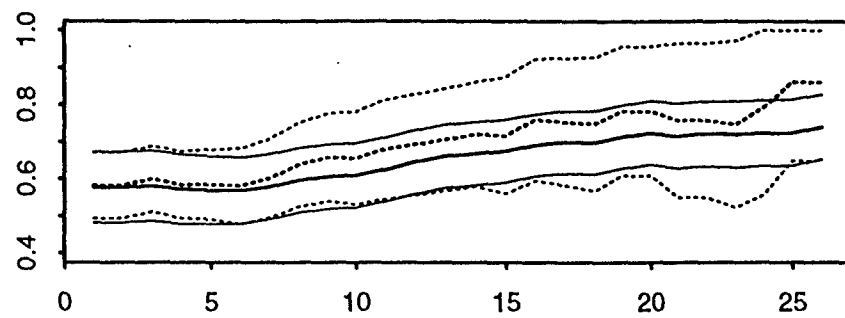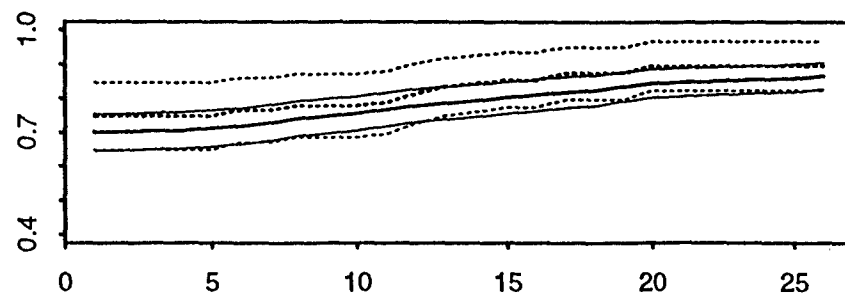
Figure 6: One Year Leukemia-Free Survival Probabilities with 95% Confidence Intervals: Proportional Hazards Model (solid line) vs. Andersen Model (dotted line)

GROUPED FAILURE TIMES
TIED FAILURE TIMES

*TWO CONTRIBUTIONS TO THE
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GROUPED FAILURE TIMES

In many investigations for life times, data are grouped prior to their statistical analysis. The grouped survival data consists of occurrence and exposure data over given time intervals and possible covariate strata. For grouped failure times there is an assumed continuous underlying hazard function in contrast to discrete failure time data (Fahrmeir [13]) with an intrinsically discrete time variable, discrete hazards, survival functions etc.

One of the primary reasons for grouping can be found in studies involving large sample sizes such as epidemiologic studies (Breslow [6]). Such studies typically involve the follow-up of large population groups over certain time periods to assess the cause and rate of death and/or to compare death rates among different population groups. Grouping data from such large sample sizes into tabular presentations (life tables) often provides a convenient format for presenting and summarizing life information. Also grouping could be done intentionally, e.g. to economize on data transmission and storage, to reduce computation, to protect the privacy of individual records, or to account for the limitations of a measurement instrument. Moreover, some large data sets are publicly released only in grouped form, as discussed by Haitovsky ([19], [20]). Some examples that illustrate such grouped survival data are: the American Cancer Society study of 1,000,000 men and women (Hammond [18]) to determine the dose-time-response relationships between smoking and lung cancer or heart disease and the life span study of over 100,000 Japanese atom bomb survivors in Hiroshima and Nagasaki (Beebe [4]).

Another important reason for grouping data is that it is often difficult or even impossible to obtain exact life time, because ethical, physical or economic restrictions in research design allow the subjects in the follow-up study to be monitored only periodically. Thus, this type of study only provides the grouped information, i.e., the exact failure time is unknown and the only available information is whether the event of interest occurred between two inspection times. The following study illustrate situations where periodic inspection is used: The National Labor Survey of Youth (NLSY) study of time to weaning of breast-fed newborns in which 927 first-born children of mothers who chose to breast feed their children were interviewed yearly.

Similar to continuous data in survival analysis, grouped survival data can involve censored data (right censoring, left censoring or double censoring) and/or truncated data. Moreover, the exact censoring or truncation times may be unknown for grouped data. For example, in the study of time to weaning of breast fed newborns, some infants are lost follow-up and some infants were withdrawn from the study without being weaned. Also grouped survival data can involve covariates (explanatory variables). Some parametric hazard models and the well-known Cox's proportional hazards model are often fitted to grouped survival data (Prentice and Gloeckler [37]).

1

The vast literature on grouped survival data involves: deriving the estimators of the hazard function and survival function under nonparametric or parametric models, test statistics for comparing the survival probabilities among different population groups, and large sample properties for these estimators and test statistics. Most estimates are derived based on maximum likelihood methods. Some references to such studies will be given later. The Bayesian approach to analyzing grouped survival data has also been studied in the literature (see Cornfield and Detre [8]; Johnson and Christensen [27]).

Notation of Grouped Survival Data

Let time be partitioned into a fixed sequence of intervals $\mathcal{T}_1, \mathcal{T}_2, \cdots, \mathcal{T}_m$ with $\mathcal{T}_j = (t_{j-1}, t_j]$ and $0 = t_0 < t_1 < \cdots < t_m \leq \infty$. For grouped failure time data the only available information is:

n_j = number of subjects entering $\mathcal{T}_j$ not having experienced the event,

d_j = number of individuals experiencing the event in $\mathcal{T}_j$,

w_j = number of individuals lost to follow-up or withdrawn during $\mathcal{T}_j$,

μ_j = number of individuals left truncated during $\mathcal{T}_j$,

Y_j = total time of individuals at risk during $\mathcal{T}_j$.

Note that all $\mu_j = 0$ when no left truncation occurs. Also, when the subjects are monitored periodically, the total time at risk Y_j is unknown. It is often approximated by $Y_j \approx [n_j - (d_j + w_j)/2](t_j - t_{j-1})$ for right censored data.

Life Table

The life table is one of the oldest and most commonly used methods of presenting lifetime data. It is a table for presenting and summarizing data, and estimating the survival function, the probability density function and the hazard function along with the variance of these estimators. For more details on the life table, see Gehan [17], Breslow[7] and Hoem [22].

Interval Censored Grouped Data

For the interval (doubly) censored grouped data, Turnbull ([40], [41]) proposed an "self-consistency" procedure, developed by Efron [11], to estimate the survival function $S(t)$. The Turnbull Estimator is a nonparametric maximum likelihood estimator (NPMLE). Frydman [16] discussed derivation and asymptotic properties of the Turnbull Estimator. Sun [39] discussed some alternative approaches to maximizing the NPMLE.

Log-Rank Test

Comparison of the survival probabilities with treatment groups or covariate strata in the grouped data can be done through rank tests. In the continuous data case Fleming and Harrington [14] studied a class of weighted log-rank tests. These weighted log-rank tests can be extended to the grouped failure time data. The usual log-rank test (or evenly weighted log-rank test) is most commonly and widely used in practice. Here we discuss the grouped data version of the log-rank test. First, let's consider the two sample case. Let n_{ij} and d_{ij}, $j = 1, \cdots, m, i = 1, 2$, be the number at risk at begining of jth interval and observed failures in jth interval, respectively, in sample i. Take n_j and d_j to be the corresponding values in the combined sample. The data can be summarized as

	Sample		
Failure	1	2	Total
Yes	d_{1j}	d_{2j}	d_j
No	$n_{1j} - d_{1j}$	$n_{2j} - d_{2j}$	$n_j - d_j$
Total	n_{1j}	n_{2j}	n_j

corresponding to the jth time interval. The grouped data based two sample log-rank test can be computed as

$$
Q = \left\{ \sum_{j=1}^{m} (d_{1j} - E_{1j}) \right\}^2 \bigg/ \left\{ \sum_{j=1}^{m} V_{1j} \right\},
$$

where E_{1j} and V_{1j} are the expected value and variance of d_{1j}, given by

$$
E_{1j} = \frac{d_j n_{1j}}{n_j}, \quad \text{and} \quad V_{1j} = \frac{d_j n_{1j} n_{2j} (n_j - d_j)}{n_j^2 (n_j - 1)}.
$$

Under the hypothesis of $S_1(t) = S_2(t)$, the two-sample log-rank test statistic Q has approximately the chi-squared distribution with 1 degree of freedom when the sample sizes are moderately large for each sample.

We can extend the two-sample log-rank test to the k-sample comparison. The k-sample log-rank test has a quadratic form with $(d_{1j} - E_{1j})$ replaced by the corresponding values from $(k - 1)$ samples and with V_{1j} replaced by the corresponding covariance matrix, where the (hl)th element is

$$
\hat{\sigma}_{hl} = \frac{d_j n_{hj}}{n_j} \left(\delta_{hl} - \frac{n_{hj}}{n_j} \right) \frac{(n_j - d_j)}{(n_j - 1)},
$$

and δ_{hl} is a Kronecker delta, i.e., $\delta_{hl} = 1$ if $h = l$, and 0 otherwise.

Parametric Models and Regression Analysis

In survival analysis some parametric models have been studied extensively. The common parametric distributions considered are Exponential, Gamma, Weibull, Log Normal and Gompertz distributions. These parametric models are often fitted to grouped data as well. The parameters are usually estimated by maximizing the full (unconditional) likelihood or the conditional likelihood. That is the likelihood function for the interval $(t_{j-1}, t_j]$ conditional on surviving till t_{j-1}. Many authors have given grouped data version MLE, see Elandt-Johnson and Johnson [12], Lawless [30] and Deddens and Koch [10]. Turnbull [42] studied a likelihood ratio statistic for testing goodness of fit for grouped failure data with possible doubly censoring.

It is important to assess the effects of covariates that may be associated with the lifetimes in many applications of survival analysis. The regression model for the conditional hazard function $\lambda(t|z)$ of the failure time given covariate z could be used to examine the covariate effects. Continuous covariates are often grouped into a fixed number strata and the value for the strata is approximated by the midpoint of the covariate in the stratum. For simplicity we consider a one dimensional covariate case. The methods and results discussed here can be extended to multidimensional cases. Let the cells into which the data are grouped be denoted $\mathcal{C}_{rj} = \mathcal{T}_r \times \mathcal{I}_j$, where $\mathcal{T}_1, \ldots, \mathcal{T}_{L_n}$ and $\mathcal{I}_1, \ldots, \mathcal{I}_{J_n}$ are the respective calendar periods (time intervals) and covariate strata. Grouped failure time data consist of the total number of failures (occurrence) and the total time at risk (exposure) in each cell $\mathcal{C}_{rj}$, given by d_{rj} and Y_{rj}. In the literature, most early work has been done under the piecewise exponential model, i.e., the hazard function is assumed to be piecewise constant within each grouping cell. The natural estimate of the unknown hazard rate λ_{rj} is $\hat{\lambda}_{rj} = d_{rj}/Y_{rj}$ (occurrence/exposure rate). Deddens and Koch [10] showed that the maximum likelihood is approximately equivalent to maximizing the piecewise exponential likelihood function

$$L = \prod_{r,j} \lambda_{rj}^{d_{rj}} \{\exp(-\lambda_{rj} Y_{rj})\}.$$

The occurrence/exposure rate estimator can also be obtained by solving the equations of $\partial \log L / \partial \lambda_{rj} = 0$.

The counting process approach and martingale techniques are applicable in grouped failure time data analysis. We assume that the counting process N_i, where $N_i(t)$ is the number of failures of the ith individual during time period $[0, t]$, has intensity

$$\lambda_i(t) = Y_i(t) \lambda(t, Z_i(t)),$$

4

where $Y_i(t)$ is a predictable $\{0,1\}$-valued process indicating that the ith individual is at risk with $Y_i(t) = 1$, and $Z_i(t)$ is a predictable covariance process. The occurrence and exposure in each cell $\mathcal{C}_{rj}$ can be written as

$$d_{rj} = \sum_i \int_{\mathcal{T}_r} I\{Z_i(t) \in \mathcal{I}_j\} dN_i(t) \quad \text{and} \quad Y_{rj} = \sum_i \int_{\mathcal{T}_r} I\{Z_i(t) \in \mathcal{I}_j\} Y_i(t) dt.$$

When the censoring processes are independent of the survival time, we can show that $M_i(t) = N_i(t) - \int_0^t \lambda_i(u) du$ are local martingales. Under the piecewise constant model ($\lambda(t,z) = \lambda_{rj}$, for $(t,z) \in \mathcal{C}_{rj}$),

$$\hat{\lambda}_{rj} = \frac{d_{rj}}{Y_{rj}} = \frac{M_{rj}}{Y_{rj}} + \lambda_{rj} \frac{Y_{rj}}{Y_{rj}},$$

where $M_{rj} = \sum_i \int_{\mathcal{T}_r} I\{Z_i(t) \in \mathcal{I}_j\} dM_i(t)$ is the martingale part of d_{rj}. Since each $t \in \mathcal{T}_r$, Y_{rj} is not predictable, the martingale techniques are not applicable directly. However, under the iid cases and some mild conditions, we can show that there exists a piecewise constant function f_{rj} bounded away from zero such that $n^{-1} Y_{rj}$ converges to f_{rj} in probability. Then we can replace M_{rj}/Y_{rj} by $M_{rj}/n f_{rj}$ with the difference of $o_P(1)$. It follows that

$$\hat{\lambda}_{rj} = \frac{M_{rj}}{n f_{rj}} + \lambda_{rj} + o_P(1),$$

and the predictable variation process of M_{rj}/f_{rj} is

$$\left\langle \frac{M_{rj}}{f_{rj}} \right\rangle = \frac{\lambda_{rj} Y_{rj}}{f_{rj}^2}.$$

Therefore, $\hat{\lambda}_{rj}$ is an asymptotic unbiased estimator and the variance can be consistently estimated by

$$\hat{\sigma}_{rj} = \widehat{\text{Var}}(\hat{\lambda}_{rj}) = \frac{d_{rj}}{(Y_{rj})^2}.$$

For the general nonparametric model where the hazard function is unspecified, Holford [23] noted that this estimator is inconsistent unless the grouping becomes finer as the sample size increases.

The useful models for many applications are the multiplicative and additive risk model. The model equations are given by

$$\lambda_{rj} = \lambda_{r0} \exp(\beta z_j) \quad \text{and} \quad \lambda_{rj} = \lambda_{r0} + \beta z_j,$$

where λ_{r0} is the baseline hazard rate of the rth time period. The parameters λ_{r0} and β are readily estimated by the MLE. Berry [5] and Frome [15] provide explicit

MLE for this approach. For the multiplicative risk model the hazard function can be written as $\lambda_{rj} = \exp(\alpha_i + \beta z_j)$ which has a log-linear form. It is often called the log linear piecewise constant model. Holford [24] derived the log likelihood for this model:

$$L = \sum_r \alpha_r d_r. + \sum_{r,j} d_{rj}\beta z_j - \sum_{r,j} Y_{rj}\exp(\alpha_r + \beta z_j),$$

where $d_r. = \sum_{j=1}^{J_n} d_{rj}$ is the number of failures in the rth calendar period. Taking derivatives of L with respect to α_r and β and setting them equal to zero, the MLE estimator of β is given by solving the following equation:

$$\sum_{r,j} z_j d_{rj} - \sum_r \frac{\sum_j Y_{rj}z_j \exp(\beta z_j)}{\sum_j Y_{rj}\exp(\beta z_j)} d_r. = 0.$$

As we discuss later, this MLE estimator of β also can be obtained by maximizing the grouped data version of Cox's partial likelihood.

The more general models are: Cox's proportional hazards model (Cox [9]) where $\lambda(t,z) = \lambda_0(t)\exp(\beta z)$, and Aalen's additive risk model (Aalen [1]) where $\lambda(t,z) = \lambda_0(t) + \beta(t)z$.

Cox's proportional hazards model has so far been the most popular model in survival analysis. The parameter estimator $\hat{\beta}$ is obtained by maximizing Cox's partial likelihood function. Andersen and Gill [3] provide an excellent proof that $\sqrt{n}(\hat{\beta} - \beta_0) \xrightarrow{P} N(0, V)$, where V^{-1} is consistently estimated by $-n^{-1}\partial U(\hat{\beta})/\partial\beta$ and U is the partial likelihood score function $U(\beta) = \partial \log L(\beta)/\partial\beta$. The grouped data based estimator $\hat{\beta}_g$ can be obtained by maximizing the following approximation to the partial likelihood:

$$L_g(\beta) = \prod_{r,j} \left\{ \frac{e^{\beta z_j}}{\sum_k Y_{rk}e^{\beta z_k}} \right\}^{d_{rj}}$$

where the product is over the grouping cells, the sum is over the covariate strata, and z_j is the midpoint of the jth covariate stratum. This estimator has been studied by Kalbfleisch and Prentice [28], Holford [23], Prentice and Gloeckler [37], Breslow [6], Hoem [21], Selmer [38], and Huet and Kaddour [25]. It can be interpreted as the maximum likelihood estimator in a Poisson regression model, as shown by Laird and Olivier [29]. Under slightly stronger regularity conditions proposed in Andersen and Gill [3], it can be shown that $\sqrt{n}(\hat{\beta}_g - \beta_0) \xrightarrow{P} N(0, V)$, when the time intervals and covariate strata shrink at some suitable rate as the sample size increases. It is important to be able to assess estimation bias caused by grouping and to correct it if necessary. In the general grouped data analysis, A 'Sheppard correction' can be used to reduce the bias to a higher order of the interval width, see Lindley [31]. McKeague and Zhang [36] obtained a Sheppard correction for Cox's proportional

hazards model, provided a consistent estimator for Sheppard correction, and derived the optimal rate of convergence for $\hat{\beta}_g$. The grouped data based estimator of the baseline hazard function, λ_0, is

$$\hat{\lambda}_0(t) = \frac{\sum_j d_{rj}}{\sum_j Y_{rj} e^{\hat{\beta}_g z_j}} \quad \text{for } t \in \mathcal{T}_r.$$

Aalen's additive risk model provides a useful and sometimes biologically more plausible alternative to the Cox proportional hazards model. For continuous data, Aalen proposed a least squares estimator for the cumulative hazard functions which has been studied by Aalen ([1], [2]), Mau ([32], [33]), and McKeague [34]. McKeague [35] and Huffer and McKeague [26] fit Aalen's additive risk model to the grouped data (when the covariates are observed for each individual and are non-time dependent), and studied asymptotic results for the grouped data version of the least squares estimator and weighted least squares estimator. The estimators can be generalized to the more general grouped data setting where the only available information is d_{rj} and Y_{rj} for each cell $\mathcal{C}_{rj}$. More work is needed.

Finally, fitting parametric and regression models to grouped failure time data is based on d_{rj} and Y_{rj}. As we discussed in the univariate case, Y_{rj} may not be observable in some applications. It is usually approximated by $Y_{rj} \approx (n_{rj} - (d_{rj} + w_{rj})/2)l_r$, where n_{rj} is the number of individuals at risk at beginning of the time period $\mathcal{T}_r$ for the jth covariate stratum, w_{rj} is the number of individuals who withdrew in cell $\mathcal{C}_{rj}$, and l_r is the width of the time interval $\mathcal{T}_r$. This approximation is based on the assumption that, on the average, the individuals failed or withdrew at middle of the each time period. However, in most applications, this assumption does not hold true. The bias introduced by this approximation could be severe. Cautions must be taken when grouping the data so that the number of grouping cells are sufficiently large (the width of time periods and covariate strata are relative small), and each grouping cell contains sufficient individuals at risk.

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TIED FAILURE TIMES

Tied failure times frequently occur in survival studies. Although theoretically a lifetime is a continuous variable, in practice it is often measured to a degree of fineness due to measurement limitation, the way failure times are recorded, or the expense of more accurate measurements may outweigh the value of added information. If the number of ties are substantial, discrete failure time models may need to be considered. Therefore, discrete failure time methods or grouped data techniques such as life tables should be used. However, if there are only a few ties, the regular procedures in handling continuous data may be used with some adjustment for tied observations. In the literature adjustment for ties has been proposed and studied for various statistical procedures in survival analysis. See Miller [9], Lawless [8], Kalbfleisch and Prentice [6], Peto and Peto [10], Andersen et al [1], and Klein and Moeschberger [7]. Here we will only discuss adjustment for ties for some common statistical procedures.

Consider the method of handling ties in the Kaplan-Meier or product-limit (PL) estimator of the survival function. If only one individual fails (no ties are present) at time t, then the factor for the single death in the PL estimator is $(1 - 1/Y(t))$ where $Y(t)$ counts the number of individuals at risk at time $t-$. For tied uncensored observations, suppose d failures occur at time t. Split the times of the d failures infinitesimally so that the factor for the d failures in the PL estimator is

$$\left(1 - \frac{1}{Y(t)}\right)\left(1 - \frac{1}{Y(t) - 1}\right) \cdots \left(1 - \frac{1}{Y(t) - d + 1}\right) = 1 - \frac{d}{Y(t)}.$$

If censored and uncensored observations are tied at time t, consider the uncensored individuals as having failed just before the censored observations.

In the k-sample test, the weighted log rank test statistic is

$$Z_h(t) = \int_0^t K(s) dN_h(s) - \int_0^t K(s) \frac{Y_h(s)}{Y.(s)} dN.(s),$$

for $h = 1, 2, \cdots, (k - 1)$, where K is the weight function, $N_h(s)$ and $Y_h(s)$ are the number of failures during time period $[0, s]$ and number of individuals at risk prior to time s for hth sample, respectively, and $N. = \sum_h N_h, Y. = \sum_h Y_h$. The covariance of $(Z_h(t), Z_j(t))$ may be estimated consistently by

$$\hat{\sigma}_{hj} = \int_0^t K^2(s) \frac{Y_h(s)}{Y.(s)} \left(\delta_{hj} - \frac{Y_j(s)}{Y.(s)}\right) dN.(s),$$

where δ_{hj} is a Kronecker delta, i.e., $\delta_{hl} = 1$ if $h = l$, and 0 otherwise. In the presence of tied observations, the covariance of $(Z_h(t), Z_j(t))$ needs to be adjusted to

$$\hat{\hat{\sigma}}_{hj} = \int_0^t K^2(s) \frac{Y_h(s)}{Y.(s)} \left(\delta_{hj} - \frac{Y_j(s)}{Y.(s)}\right) \frac{Y.(s) - \Delta N.(s)}{Y.(s) - 1} dN.(s).$$

Clearly, when there are no tied observations, $\hat{\sigma}_{hj}$ and $\hat{\tilde{\sigma}}_{hj}$ coincide.

Cox's partial likelihood has been commonly used to estimate the coefficients, $\boldsymbol{\beta}$, in Cox's proportional hazards model. Let $t_1 < t_2 < \cdots < t_k$ be the k ordered event times. Let the set $\mathcal{D}_i$ consist of the d_i individuals who failed at the time t_i and $\mathcal{R}_i$ be the risk set prior to t_i. Denote $\boldsymbol{s}_i = \sum_{l \in \mathcal{D}_i} \boldsymbol{z}_l$. If there are ties among event times, the following adjusted partial likelihoods have been proposed:

Breslow [2] suggests a partial likelihood of

$$L_1(\boldsymbol{\beta}) = \prod_{i=1}^{k} \frac{\exp(\boldsymbol{\beta}' \boldsymbol{s}_i)}{\left[\sum_{l \in \mathcal{R}_i} \exp(\boldsymbol{\beta}' \boldsymbol{z}_l) \right]^{d_i}}.$$

Efron [5] proposed an alternative partial likelihood of

$$L_2(\boldsymbol{\beta}) = \prod_{i=1}^{k} \frac{\exp(\boldsymbol{\beta}' \boldsymbol{s}_i)}{\prod_{j=1}^{d_i} \left[\sum_{l \in \mathcal{R}_i} \exp(\boldsymbol{\beta}' \boldsymbol{z}_l) - \frac{j-1}{d_i} \sum_{l \in \mathcal{D}_i} \exp(\boldsymbol{\beta}' \boldsymbol{z}_l) \right]}.$$

The third partial likelihood due to Cox [3] is based on a discrete time hazard rate model. The discrete logistic likelihood is

$$L_3(\boldsymbol{\beta}) = \prod_{i=1}^{k} \frac{\exp(\boldsymbol{\beta}' \boldsymbol{s}_i)}{\sum_{\boldsymbol{q} \in \mathcal{Q}_i} \exp(\boldsymbol{\beta}' \boldsymbol{s}_q^*)},$$

where $\mathcal{Q}_i$ is the set of all subsets of d_i individuals who could be selected from the risk set $\mathcal{R}_i$ and $\boldsymbol{s}_q^* = \sum_{j=1}^{d_i} \boldsymbol{z}_{q_j}$.

The fourth alternative partial likelihood is (see DeLong et al [4])

$$L_4(\boldsymbol{\beta}) = \prod_{i=1}^{k} \left\{ \int_0^{\infty} \prod_{j=1}^{d_i} \left[1 - \exp\left(-\frac{\exp(\boldsymbol{\beta}' \boldsymbol{z}_j)}{\sum_{l \in \mathcal{R}_i^*} \exp \boldsymbol{\beta}' \boldsymbol{z}_l)} t \right) \right] \exp(-t) dt \right\},$$

where $\mathcal{R}_i^* = \mathcal{R}_i \backslash \mathcal{D}_i$ is the set of individuals whose event or censored times exceed t_i or whose censored times are equal to t_i. It is often called exact likelihood.

Note that when the number of ties is small, Breslow's and Efron's likelihoods are quite close. Of course, if no ties occur at the event times, all four likelihood functions reduce to the regular Cox's partial likelihood.

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1

INTRODUCTION

Many applications in biostatistics involve the modeling of lifetime data. In these applications the outcome of interest is the time T, until some event occurs. This event may be death, the appearance of a tumor, the development of some disease, recurrence of a disease, conception, cessation of smoking, and so forth. Here T is a non-negative random variable from a homogenous population.

In this article we shall examine how the distribution of T can be characterized. Four functions characterize the distribution of T, namely, the *survival function*, which is the probability of an individual surviving beyond time t, the *hazard rate* which is approximately the chance an individual of age t experiences the event in the next instant in time, the *probability density (or mass) function*, which is the approximate unconditional probability of the event occurring at time t, and the *mean residual life* at time t, which is the mean time to the event of interest, given the event has not occurred at t. If we know any one of these four functions, then the other three can be uniquely determined. These functions are introduced for continuous, discrete and mixed random variable in the following sections and the interrelationship among the four functions are discussed.

The distribution of the time to an event can also be characterized by the aging properties of the distribution of T. Aging classes are based on certain properties of one of the four basic quantities that describe the distribution

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of T. These classes are defined and some basic properties of these classes are discussed in the final section.

THE SURVIVAL FUNCTION

The basic quantity employed to describe time-to-event phenomena is the survival function. This function, also known as the survivor function or survivorship function, is the probability an individual survives beyond time t. It is defined as

$$S(t) = Pr\,[T \geq t]\,.$$

In the context of equipment or manufactured item failures, $S(t)$ is referred to as the reliability function. Note that the survival function is a non increasing function with a value of 1 at the origin and 0 as t approaches infinity.

If T is a continuous random variable then $S(t)$ is a continuous monotone decreasing function and the survival function is the complement of the cumulative distribution function $F(t) = Pr\,[T \leq t]$. That is $S(t) = 1 - F(t)$. The survival function is the integral of the probability density function $f(t)$. That is,

$$S(t) = Pr\,(T \geq t) = \int\limits_{t}^{\infty} f(u)du$$

Thus, we have the following relationship:

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$$f(t) = -\frac{dS(t)}{dt}.$$

Note that $f(t)\Delta t$ may be thought of as the "approximate" probability of the event occurring at time t and that $f(x)$ is a non-negative function with the area under $f(x)$ being equal to one.

Example

A common distribution used in many applications in the Weibull distribution with probability density function $f(t) = \lambda \alpha t^{\alpha-1} \exp\left(-\lambda t^{\alpha}\right), \lambda > 0, \alpha > 0$. The exponential distribution is a special case of the Weibull distribution when $\alpha = 1$. The survival function for the Weibull distribution is $S(t) = \exp(-\lambda t^{\alpha}), \lambda > 0, \alpha > 0$. Survival curves with a common median of 6.93 are exhibited in Figure 1 for $\lambda = .26328$, $\alpha = .5$; $\lambda = .1$, $\alpha = 1$; and $\lambda = .00208, \alpha = 3$. $\Diamond$

When T is a discrete random variable then the survival function is a non increasing left-continuous step function. If T can take on values $t_0 < t_1 < t_2 < \ldots$ with probability mass function (p.m.f.) $p(t_j) = \Pr\left(T = t_j\right), j = 1, 2, \ldots$ then

$$S(t) = Pr\left(X \geq t\right) = \sum_{j: t_j \geq t} p(t_j).$$

Note that the survival function and probability mass function are related by

$$p(t_j) = S(t_j) - S(t_{j+1})$$

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. Here we have defined $S(t) = Pr[T \geq t]$ as was the case in [3] and [4]. This definition was used to make later formulas for the discrete case simpler. Other authors (c.f. [5] and [6]) have defined $S(t) = Pr[T > t]$ which makes the relationship $S(t) = 1 - F(t)$ hold for both the discrete and continuous case.

THE HAZARD FUNCTION

A basic quantity, foundational in survival analysis, is the hazard function. This function is also known as the conditional failure rate in reliability, the force of mortality in demography, the age-specific failure rate in epidemiology, the inverse of the Mill's ratio in economics or simply as the hazard rate. The hazard rate is defined as

$$h(t) = \lim_{\Delta t \to 0} \frac{Pr[t \leq T < t + \Delta t | T \geq t]}{\Delta t}. \tag{1}$$

The hazard rate is a non-negative function. It tells us how quickly individuals of a given age are experiencing the event of interest. The quantity $h(t) \Delta t$ is the approximate probability that an individual who has survived to age t will experience the event in the interval $(t, t + \Delta t)$.

This function is particularly useful in determining the appropriate failure distributions utilizing qualitative information about the mechanism of failure and for describing the way in which the chance of experiencing the event changes with time. There are many general shapes for the hazard rate. Some

generic types of hazard rates are increasing, decreasing, constant, bathtub-shaped or hump-shaped hazard rates. Models with increasing hazard rates arise when there is natural aging or wear-out. Decreasing hazard functions are much less common but find occasional use when there is a very early likelihood of failure such as in certain types of electronic devices or in patients experiencing certain types of transplants. Decreasing hazard rates often arise as models for heterogenous populations where the hazard rates of members of the population are random (See Frailty models). Most often a bathtub-shaped hazard is appropriate in populations followed from birth. Most population mortality data follows this type of hazard function where, during an early period, deaths result primarily from infant diseases after which the death rate stabilizes followed by an increasing hazard rate due to the natural aging process. Finally, if the hazard rate is increasing early and eventually begins declining, then the hazard is termed hump-shaped. This type of hazard rate is often used in modeling survival after successful surgery where there is an initial increase in risk due to infection, hemorrhaging, or other complications just after the procedure, followed by a steady decline in risk as the patient recovers.

If T is a continuous random variable, then

$$h(t) = f(t)/S(t) = -\frac{d\ln[S(t)]}{dt}$$

A related quantity is the cumulative hazard function $H(t)$, defined by

$$H\left(t\right) = \int_0^t h(u)du = -\ln\left[S\left(t\right)\right].$$

Thus for continuous lifetimes we have the following relationship:

$$S\left(t\right) = \exp\left\{-H\left(t\right)\right\} = \exp\left\{-\int_0^t h(u)du\right\}.$$

One particular distribution, which is flexible enough to accommodate increasing $(\alpha > 1)$, decreasing $(\alpha < 1)$, or constant hazard rates $(\alpha = 1)$, is the Weibull distribution. Hazard rates, $h(x) = \alpha\,\lambda\,x^{\alpha-1}$, are plotted in Figure 2 for the Weibull distribution with $\lambda = .26328, \alpha = .5; \lambda = .1, \alpha = 1$; and $\lambda = .00208, \alpha = 3$. One can see that, though the three survival functions have the same basic shape, the three hazard functions are dramatically different. $\Diamond$

When T is a discrete random variable, the hazard function is

$$h\left(t_j\right) = \Pr\left(T = t_j | T \geq t_j\right) = \frac{p\left(t_j\right)}{S\left(t_j\right)},\ j = 1, 2, \ldots$$

Since $p\left(t_j\right) = S\left(t_j\right) - S\left(t_{j+1}\right)$ we have

$$h\left(t_j\right) = 1 - S\left(t_{j+1}\right)/S\left(t_j\right),\ j = 1, 2, \ldots$$

so that the survival function is related to the hazard function by

$$S\left(t\right) = \prod_{j:t_j<t}\left[1 - h\left(x_j\right)\right].$$

For discrete lifetimes the "cumulative hazard" function is defined by

$$H\left(t\right) = \sum_{j:t_j<t} h\left(t_j\right). \tag{2}$$

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Notice that for this definition the relationship $S(t) = \exp[-H(t)]$ no longer holds true. Some authors (Cox and Oakes [3]) prefer to define the cumulative hazard for discrete lifetimes, as

$$H(t) = \sum_{t_j < t} \ln[1 - h(t_j)], \tag{3}$$

Note that for this definition the relationship for continuous lifetimes, $S(t) = \exp[-H(t)]$ will then be preserved for discrete lifetimes. If the $h(t_j)$ are small, (2) will be a first order approximation to (3).

The hazard rate is well-defined quantity for the case where T has both discrete and continuous components. In this case the hazard function defined by (1) will have a continuous part, $h_c(t)$ and a discrete part with mass h_j at time $t_1 < t_2 < \dots$. The survival function in this case can be expressed as

$$S(t) = \exp\left\{-\int_0^t h_c(u)du\right\} \prod_{j: t_j < t} (1 - h_j)$$

For any survival function one can express the relationship between the hazard rate and the survival function by the using the notion of a product integral. For a function, G(), define the product integral of $1 - dG(u)$ over the range a to b by

$$P_a^b[1 - dG(u)] = \lim \prod_{k=1}^{r} \{1 - [G(u_k) - G(u_{k-1})]\},$$

where $a = u_1 < \dots < u_r = b$ and the limit is taken as $r \to \infty$ and $u_k - u_{k-1} \to 0$. Here G is a function of locally bounded variation which is continuous from

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the right and have finite left hand limits. If we define the cumulative hazard rate as

$$H(t) = \int\limits_0^t h_c(u)du + \sum_{j:t_j < t} h_j$$

then the survival function in the continuous, discrete or mixed case is given by

$$S(t) = P_0^t \left[1 - dH(u) \right].$$

Because of this property the product integral plays an important role in survival analytic techniques.

THE MEAN RESIDUAL LIFE FUNCTION

The fourth basic parameter of interest is the mean residual life at time t. This parameter measures, for individuals of age t, their expected remaining lifetime. It is defined as

$$mrl(t) = E(T - t | T \geq t).$$

It can be shown, using integration by parts or a partial summation formula, that the mean residual life is the area under the survival curve to the right of t divided by $S(t)$. Note that the mean life, $\mu = mrl(0)$, is the total area under the survival curve.

For a continuous random variable we have

$$mrl(t) = \frac{\int\limits_t^\infty (u-t)f(t)du}{S(t)} = \frac{\int\limits_t^\infty S(u)\, dt}{S(t)}$$

and

$$\mu = E(T) = \int\limits_0^\infty uf(u)du = \int\limits_0^\infty S(u)du.$$

Also the variance of T is related to the survival function by

$$Var(T) = 2\int\limits_0^\infty uS(u)du - \left[\int\limits_0^\infty S(u)du\right]^2.$$

In some applications the median residual life, rather then the mean residual life is of interest. To define this quantity recall that the 100pth percentile of a random variable X with cumulative distribution function (survival function) $F(x)$ ($S(x)$) is the value x_p such that

$$F(x_p) \geq p \quad \text{and} \quad S(x_p) \geq 1 - p.$$

The median lifetime is the 50th percentile, $x_{.5}$, of the distribution of X. If X is a continuous random variable then the pth quantile is found by solving the equation $S(x_p) = 1 - p$. It follows that the median lifetime, for a continuous random variable X, is the value $x_{.5}$ such that

$$S(x_{.5}) = 0.5.$$

The median residual life time of T at time t, $mdrl(t)$, is defined as the median time to the event for an individual who has survived to time t. That is, $mdrl(t)$ is solution to the equation

$$\frac{S(mdrl(t))}{S(t)} = .5.$$

The population median is simply the median residual life at time 0.

To illustrate these quantities consider the three Weibull distributions considered earlier. Figure 3 shows the mean residual life function for the Weibull models with $\alpha = 0.5, 1.0$ and 3.0. As the figure shows the mean residual life is constant for the exponential distribution ($\alpha = 1$), decreasing for the case where $\alpha = 3$ and increasing for the case where $\alpha = 0.5$. Note that the trend in the mean residual life is reversed from the trend in the hazard rate in that when the hazard rate is increasing, reflecting aging, the mean residual life is decreasing. Figure 4 depicts the median residual life functions for the three Weibull models. The shapes of the functions are quite similar to the shape of the mean residual life functions.

RELATIONSHIP BETWEEN CHARACTERIZATIONS

Interrelationships between the characterizations discussed earlier, for a continuous lifetime T, may be summarized as follows:

$$S(t) = \int\limits_{t}^{\infty} f(u)du$$

$$
\begin{aligned}
&= exp\left\{-\int_0^t h(u)du\right\} \\
&= exp\{-H(t)\} \\
&= \frac{mrl(0)}{mrl(t)} \exp\left\{-\int_0^t \frac{du}{mrl(u)}\right\};
\end{aligned}
$$

$$
\begin{aligned}
f(t) &= -\frac{d}{dt}S(t) \\
&= h(t)S(t) \\
&= \left(\frac{d}{dt}mrl(t) + 1\right)\left(\frac{mrl(0)}{mrl(t)^2}\right)\exp\left\{-\int_0^t \frac{du}{mrl(u)}\right\}
\end{aligned}
$$

$$
\begin{aligned}
h(t) &= -\frac{d}{dt}\ln[S(t)] \\
&= \frac{f(t)}{S(t)} \\
&= \left(\frac{d}{dt}mrl(t) + 1\right)/mrl(t);
\end{aligned}
$$

and

$$
\begin{aligned}
mrl(t) &= \frac{\int_t^\infty S(u)du}{S(t)} \\
&= \frac{\int_t^\infty (u-t)f(u)du}{S(t)}
\end{aligned}
$$

For a discrete random variable we have the following relationships:

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$$S(t) = \sum_{j:t_j \geq t} p(t_j)$$

$$= \prod_{j:t_j < t} [1 - h(t_j)].$$

If T is an integer valued random variable with mean residual life at time k equal to m_k, $k = 0, 1, 2, ...$ and m_0 is finite then we have

$$S(k) = \frac{1 + m_0}{m_k} \prod_{j=0}^{k} \frac{m_j}{1 + m_j}.$$

Also, for any discrete survival function, we have

$$p(t_j) = S(t_j) - S(t_{j+1})$$

$$= h(t_j)S(t_j), j = 1, 2, ...;$$

$$h(t_j) = \frac{p(t_j)}{S(t_j)},$$

and

$$mrl(t) = \frac{[t_{k+1} - t]\, S(t_{k+1}) + \sum_{j:t_j \geq t_{k+1}} [t_{j+1} - t_j]S(t_{j+1})}{S(t)}, \text{ for } t_k \leq t < t_{k+1}$$

CLASSES OF AGING DISTRIBUTIONS

An important characteristic of survival distribution is its aging properties. There are a number of classes that have been suggested in the literature to categorize distributions based on their aging properties or their dual. The

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first aging class is the class of increasing hazard rate (IHR) distributions and the dual class of decreasing hazard rate (DHR) distributions. A survival distribution is said to be in the IHR (DHR) class if and only if

$$\frac{S(t+x)}{S(t)} = S(x|t) \text{ is decreasing (increasing) in } t \text{ for all } x.$$

The definition says that the T has the IHR aging property if the probability an individual of age t survives an addition x period of time is decreasing with time. If T is a continuous random variable then an equivalent definition of the IHR (DFR) class is that the hazard rate $h(t)$ is increasing (decreasing) for all t. Examples of distributions that fall in the IHR class are the Weibull distribution with $\alpha > 1$ and the gamma distribution with shape parameter greater than one.

A second, more general aging class is the class of increasing (decreasing) hazard rate on the average, IHRA (DHRA), distributions. A distribution is said to fall in the IHRA (DHRA) class if and only if

$$-\left(\frac{1}{t}\right) \ln\left[S(t)\right] \text{ is increasing (decreasing) in } t. \tag{4}$$

The definition arises by declaring a distribution to be in the IHRA class when its cumulative hazard rate, -ln $[S(t)]$ is increasing faster than the cumulative hazard rate of an exponential random variable, t. Since the exponential distribution reflects a model with no aging, this class is one of distributions for which individuals are, on the average, aging. There are several equivalent

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definitions of a IHRA class. Since (4) implies that $S^{1/t}(t)$ is increasing in t we have that T is in the IHRA class if and only if $S(\theta t) \geq S^\theta(t)$. A second characterization of the IHRA class is that if T is in the IHRA class then for any $\lambda > 0$ the quantity $S(t) - e^{-\lambda t}$ has at most one change of sign and if it does have a change in sign then it is from $+$ to $-$. The class of IHRA distributions is larger than the class of IHR distributions in that every IHR distribution is an IHRA distribution but the converse is not true.

A third aging class is the class of decreasing (increasing) mean residual life, DMRL (IMRL) distributions. A distribution is said to be in the DMRL (IMRL) class if

$$mrl(t) = \frac{\int\limits_t^\infty S(x)dx}{S(t)} \text{ is decreasing (increasing) in } t.$$

This aging class, which include all IHR models, is one where the mean remaining life of an individual of age t is becoming shorter as t increases.

A fourth aging class is the class of new better (worse) than used NBU (NWU) distributions. Here a distribution is in the NBU (NWU) class if and only if

$$S(x + t) \leq (\geq) S(x)S(t) \text{ for any } x \text{ and } t.$$

An equivalent definition for the NBU class is

$$\frac{S(x + t)}{S(t)} = Pr\left[T \geq x + t | T \geq t\right] \leq Pr\left[T \geq x\right] = S(x).$$

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From this second definition we see that T has an NBU distribution if the probability an individual of age t lives an additional x time units is smaller than the probability an individual of age 0 survives to age x. This aging class includes all the IHRA distributions.

A fifth aging class is the class of new better (worse) that new in expectation, NBUE (NWUE) distributions. A distribution is in the NBUE (NWUE) class if its mean, μ, is finite and

$$\int_t^\infty S(u)du \leq (\geq) \mu S(t) \text{ for all } t.$$

The NBUE class is one where the mean residual life of an individual of age t is less that the mean of an individual of age 0.

A final aging class is the class of harmonic new better (worse) than used in expectation, HNBUE (HNWUE) distributions. A distribution is said to be in the HNBUE (HNWUE) class if its mean is finite and

$$\int_t^\infty S(u)du \leq \mu \exp(-t/\mu).$$

An equivalent definition for the HNBUE class is

$$\left\{ \frac{1}{t} \int_0^t \frac{dx}{mrl(x)} \right\}^{-1} \leq mrl(0).$$

This means that for a HNBUE distribution the integral harmonic value of the residual life of an individual of age t is smaller than the same quantity for a newly born individual.

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The aging classes are ordered as follows:

$$IHR \Longrightarrow IHRA \Longrightarrow NBU \Longrightarrow NBUE \Longrightarrow HNBUE$$

$$IHR \Longrightarrow DMRL \Longrightarrow NBUE \Longrightarrow HNBUE$$

$$DHR \Longrightarrow DHRA \Longrightarrow NWU \Longrightarrow NWUE \Longrightarrow HNWUE$$

$$DHR \Longrightarrow IMRL \Longrightarrow NWUE \Longrightarrow HNWUE$$

Further discussion of these failure classes can be found in Barlow and Proschan [1] and Basu and Ebrahimi [2].

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Figure 1
Comparison of Weibull Survival Functions
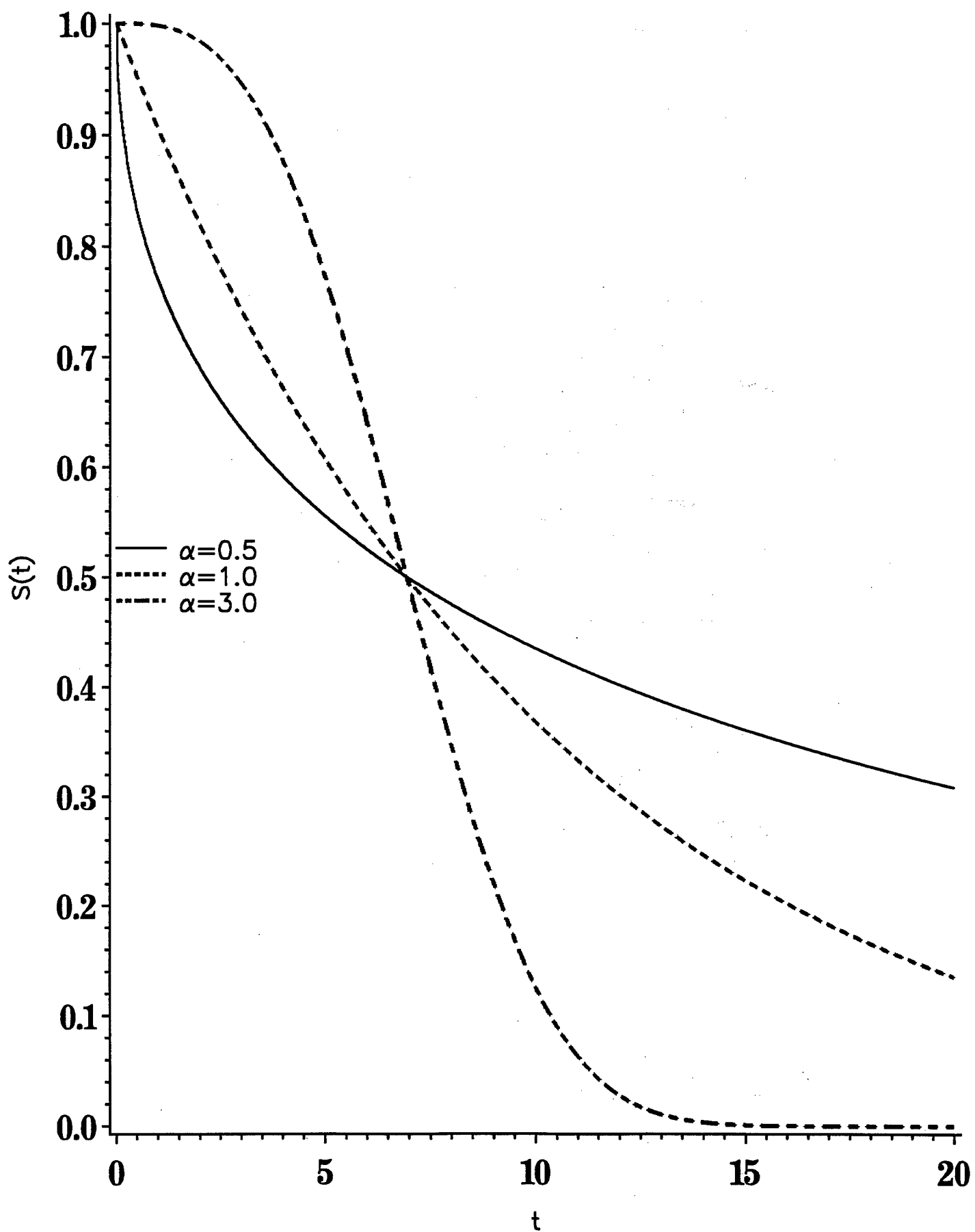
Figure 2
Comparison of Weibull Hazard Functions
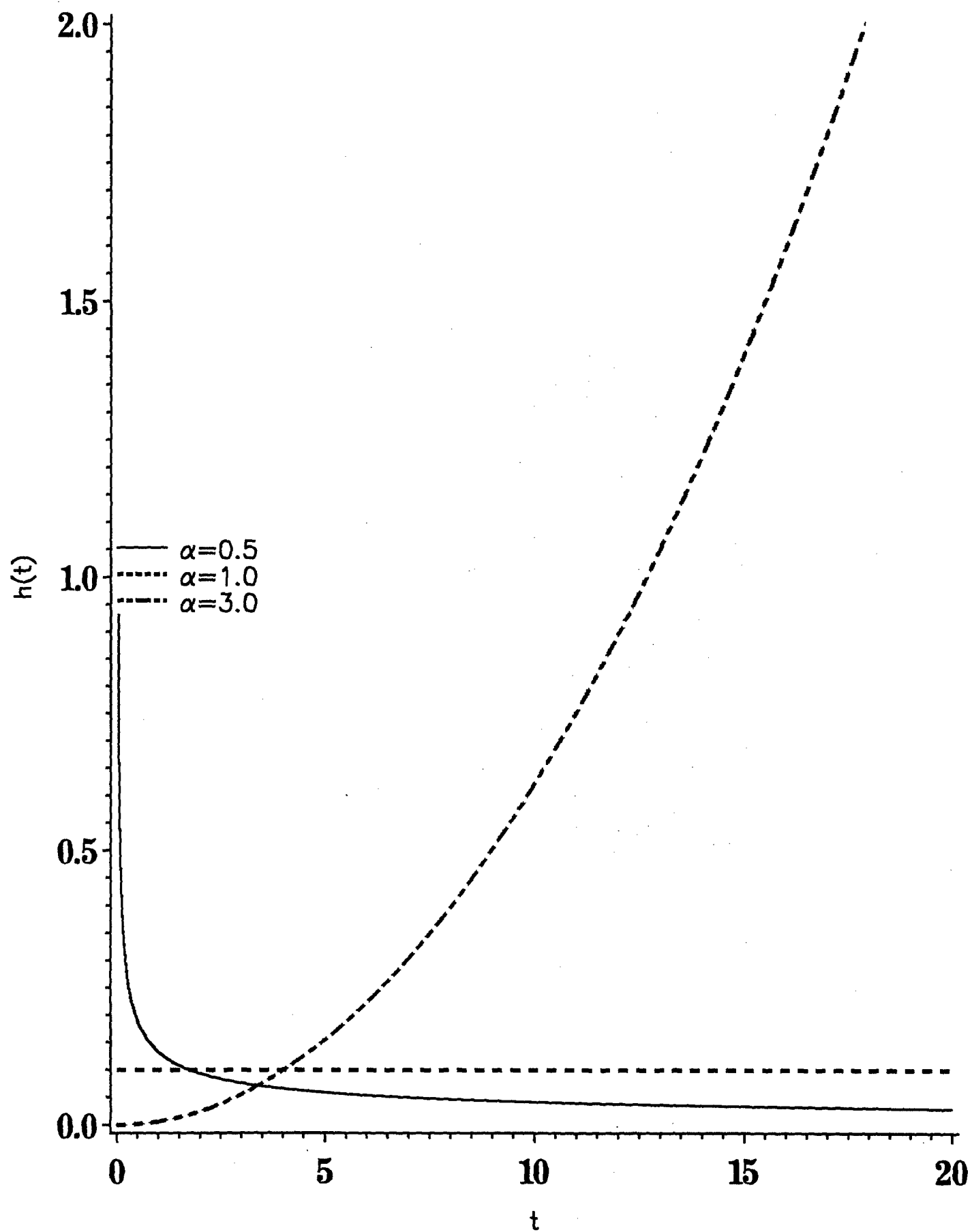
Figure 3
Comparison of Weibull Mean Residual Life Functions
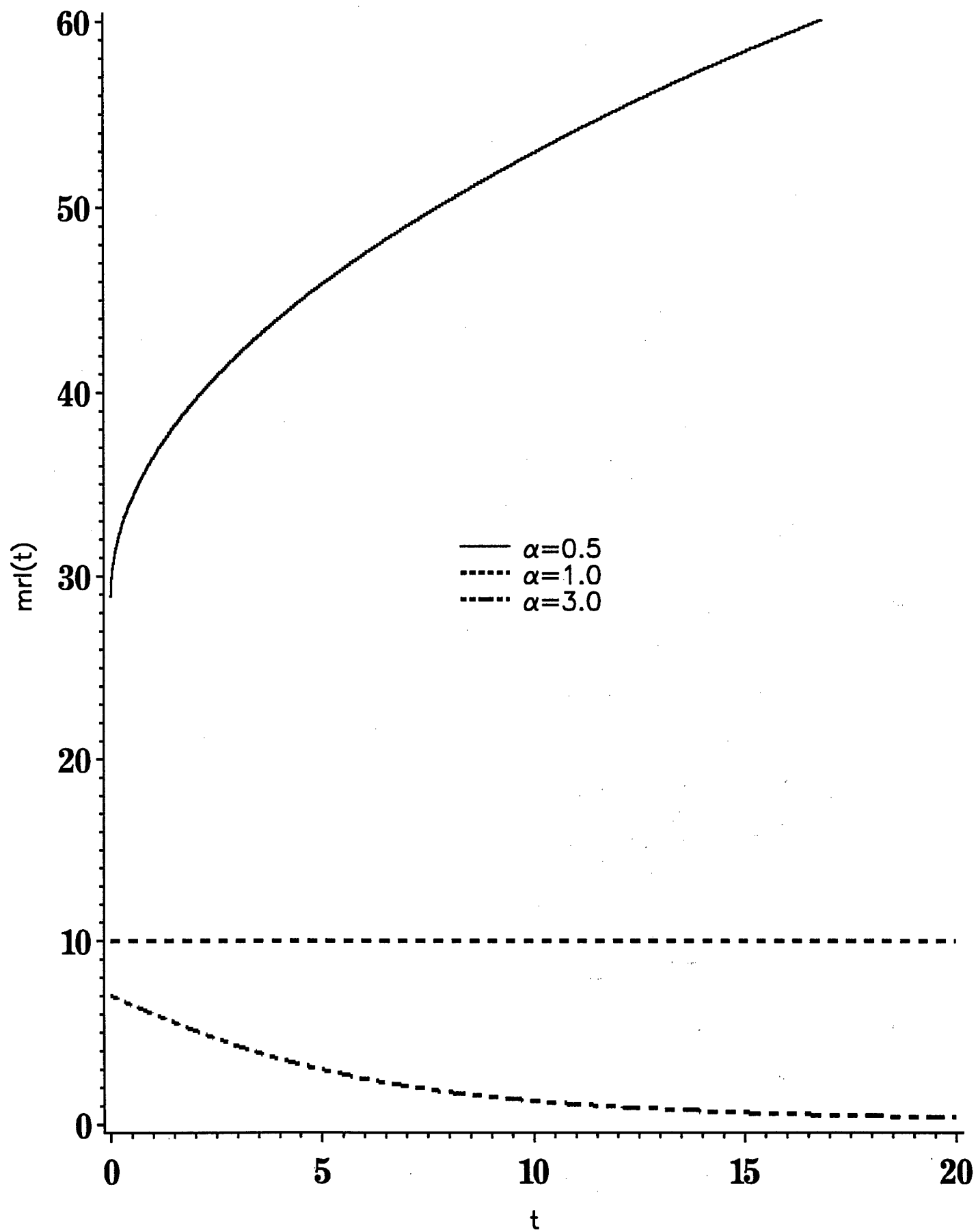
Figure 4
Comparison of Weibull Median Residual Life Functions
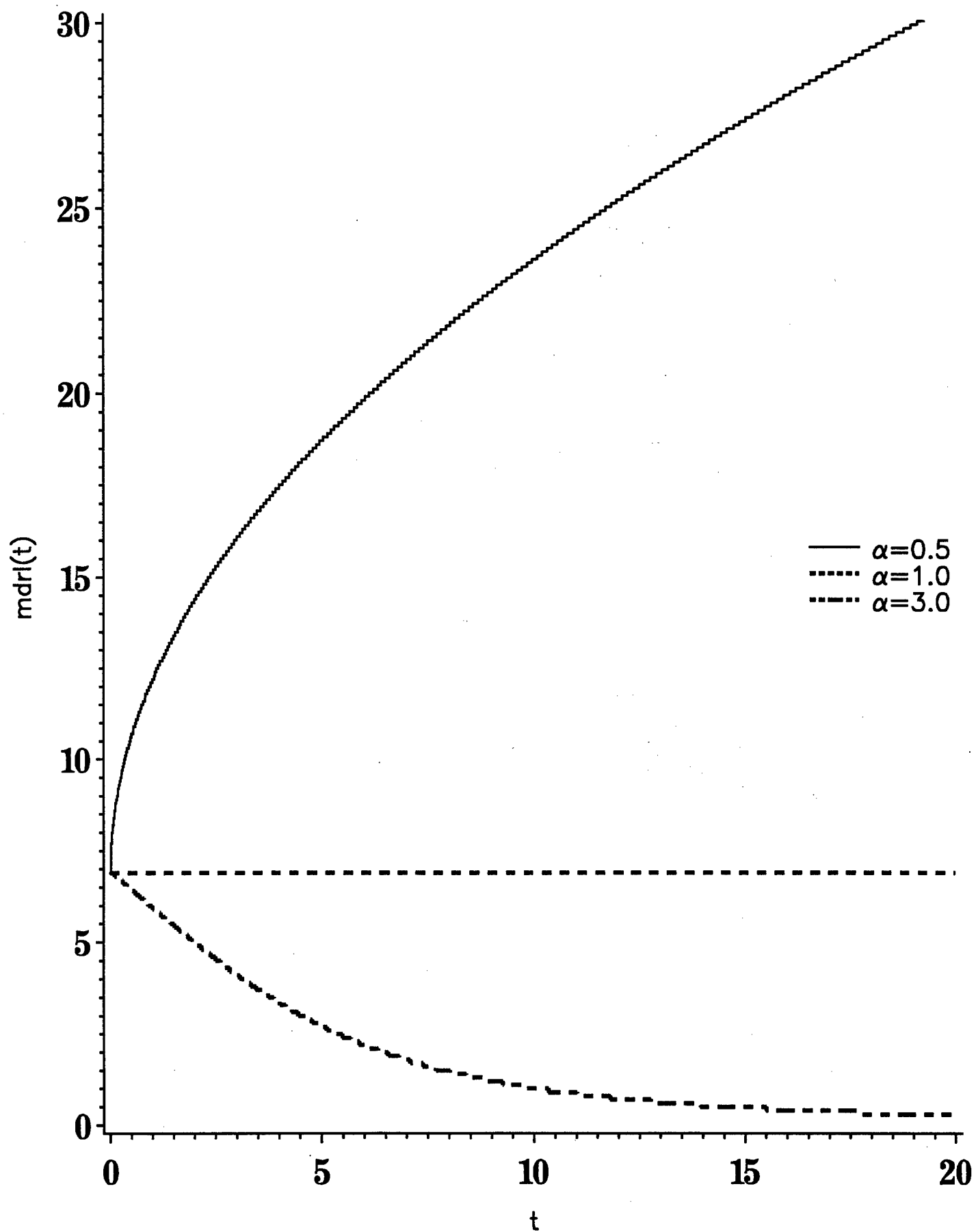
Regression Models for Survival Data

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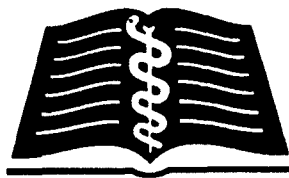
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1. INTRODUCTION

The life length or failure time of equipment or a human subject, X, can be modeled as a random variable. Frequently, however, the model for survival time can be improved by including relevant explanatory variables $Z = (Z_1, \ldots, Z_p)^t$ which are also called covariates. In our notation, Z consists of p explanatory variables. In the context of animate subjects, Z could include

(i) quantitative variables such as age, blood pressure and weight

(ii) qualitative variables such as gender, race and treatment.

Some of variables may even be time dependent in which case we write $Z(x) = (Z_1(x), \ldots, Z_p(x))^t$.

When covariates are included in the model, the primary questions of interest concern the relationship between the failure time X and the explanatory variables $(Z_1, \ldots, Z_p)^t$. For instance, this is the case when treatments need to be compared or when risk factors are identified for a particular disease.

Given the explanatory variables $Z = z$ for a subject, the failure time X will have a conditional cumulative distribution function $F(\cdot \mid z)$ which typically depends on the values of the covariates, z. We assume throughout that the conditional probability density function, $f(\cdot \mid z)$, exists. The focus of modeling is the conditional survival function or conditional hazard rate function.

$$\text{Survival function: } S(x \mid z) = P[X > x \mid z] = 1 - F(x \mid z) \tag{1.1}$$

$$\text{Hazard function: } h(x \mid z) = \frac{f(x \mid z)}{S(x \mid z)} \tag{1.2}$$

These two functions are connected by the well known relations

$$h(x \mid z) = -\frac{d\ln[S(x \mid z)]}{dx} \text{ and } S(x \mid z) = \exp\{-\int_0^x h(t \mid z)dt\} \tag{1.3}$$

There are two popular approaches to modeling the effects of covariates on survival.
1. Model the log lifetime as a classical linear model.
2. Model the conditional hazard rate.

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1.1 Models for the Log lifetime

Analogous to the classical linear regression, the first case proceeds by modeling the natural logarithm, $Y = \ln(X)$, as a linear model. That is,

$$Y = \mu + \gamma^t Z + \sigma W, \qquad (1.4)$$

where W is a random variable representing the error. This model is called the accelerated failure-time model because of the following property. When z is a vector of zero's, $X = \exp\{\mu + \sigma W\}$ and we denote its survival function by $S_0(x)$. This is the nominal or unstressed case.

Now, under the general linear model, the survival function

$$
\begin{aligned}
S(x \mid z) &= P[X > x \mid z] = P[Y > \ln x \mid z] \\
&= P[\mu + \sigma W > \ln x - \gamma^t z \mid z] \\
&= S_0(x \exp[-\gamma^t z])
\end{aligned}
\qquad (1.5)
$$

The effect of the explanatory variables is to change the time scale by the factor $\exp\{-\gamma^t Z\}$. If $\gamma^t Z$ is negative, the time to failure is accelerated. A life length x on the original unstressed scale becomes the larger length $x \exp[-\gamma^t Z]$ when the covariates have value z. If $\gamma^t Z$ is positive, time is degraded by the constant factor

In the context of testing very reliable components or systems, the $z = 0$ case corresponds to the values of variables for ordinary operating conditions. Under nominal operating conditions, it may not be unusual for no failures to occur in any reasonable length of time. Typically, then, harsher temperature, humidity, and mechanical vibrations are employed to accelerate aging and allow for some failures to be observed during a test. The values of z could then be specified as deviations from the nominal operating conditions.

Note that, for the accelerated failure-time models, the hazard rate

$$h(x \mid z) = -\frac{S'(x \mid z)}{S(x \mid z)} = h_0(x \exp[-\gamma^t Z]) \exp[-\gamma^t Z] \qquad (1.6)$$

is related to a baseline hazard rate $h_0(\cdot) = -S_0'(\cdot)/S_0(\cdot)$ and the constant change of time scale factor $\exp[-\gamma^t Z]$.

1.2 Models for the Conditional Hazard Function.

To date, the primary approach to modeling the effects of covariates on survival is to model the conditional hazard rate function in terms of covariates. Two classes of models: multiplicative hazards

models and additive hazard rate models have been used to relate the effects of the covariates on survival.

Multiplicative hazards models

The conditional hazard rate of an individual with covariate vector $Z = z$ is modeled as the product of a baseline hazard rate $h_0(x)$ and a non-negative function of the covariates $c(\beta^t z)$

$$h(x \mid z) = h_0(x) \, c(\beta^t z) \qquad (1.7)$$

In practice, the baseline hazard rate function, $h_0(x)$, may take a specified parametric form or be left as an arbitrary non negative function. The link function $c(\cdot)$ can be any non negative function but, for simplicity, the usual choice is the Cox(1972) model $c(\beta^t z) = \exp\{\beta^t z\}$

A key feature of the multiplicative hazards models is the following proportionality property. Consider the case where all of the covariates are determined at time 0 and they are fixed. Then, for two individuals with covariate values z_1 and z_2, respectively

$$\frac{h(x \mid z_1)}{h(x \mid z_2)} = \frac{h_0(x) \, c(\beta^t z_1)}{h_0(x) \, c(\beta^t z_2)} = \frac{c(\beta^t z_1)}{c(\beta^t z_2)} \qquad (1.8)$$

which is a positive constant. That is, the two hazard rate functions are proportional for all times x. When this is the case, we refer to the model (1.8) as a proportional hazards model.

In terms of the conditional survival function, applying the relation (1.3) to the model (1.7), we see that

$$S(x \mid z) = S_0(x \mid z)^{c(\beta^t z)} \qquad (1.9)$$

so the conditional survival function is the baseline survival function raised to the power $c(\beta^t z)$. In nonparametric statistics, these are known as Lehmann alternatives.

Further specializing to the Cox model, $c(\beta^t z) = \exp\{\beta^t z\}$ if the i-th individual has covariate values z we have

$$\ln[-\ln(S(x \mid z_i)] = \beta^t z_i + \ln[-\ln(S_0(x))] \qquad (1.10)$$

The logarithms of the negative logarithm of the survival functions of X, given the covariates z_i, are parallel. This relation will provide a check on the assumption of a proportional hazards model.

Additive hazard rate models

Here, the conditional hazard rate is modeled as a baseline hazard rate plus additional hazard components due to the covariates. That is,

$$h(x \mid z) = \beta_0 + \sum_{j=1}^{p} z_j(x)\beta_j(x) \tag{1.11}$$

where the regression coefficients $\beta_j(x)$, as well as the explanatory variables $z_j(x)$, are allowed to vary over time. Here β_0 is a baseline hazard rate when all the covariates are zero. The p regression functions $z_j(x)\beta_j(x)$ may be positive or negative but they are constrained so that $h(x \mid z)$ is positive.

2. CENSORING AND TRUNCATION

Before discussing inference procedures in the following sections, we first review the basic types of censoring and truncation. We also introduce the basic notation that enables us to obtain expressions for likelihoods.

We first consider Type I censoring where a lifetime X is right-censored at a fixed censoring time C_r The observation is represented by a pair of random variables (T, δ) where $T = \min(X, C_r)$ and $\delta = 1$ if failure is observed so $T = X$, and $\delta = 0$ if the observation is censored so $T = C_r$.

In the context of testing electronic units, sometimes all items may be placed on test at the same time. If the test is stopped when a specified number of failures occur, the lifetimes of the remaining units are said to be Type II censored.

A lifetime X is left-censored at a fixed censoring time C_L if it is only known to be smaller than C_L. The observation is represented by a pair of random variables (T, ε) where $T = \max(X, C_L)$ and $\varepsilon = 1$ if failure is observed so $T = X$, and $\varepsilon = 0$ if the observation is censored so $T = C_L$.

A more general form, called interval censoring occurs when it is only known that the individual's lifetime lies in an interval [L, R).

Truncation differs from censoring. When a lifetime is left-truncated at Y_L, the lifetime X will be observed only if $X \geq Y_L$. However, if $X < Y_L$ the investigator will be unaware of the individual.

We summarize the contributions to the likelihood

exact lifetimes	- $f(x)$	
right censored observations	--- $S(C_r)$	(2.1)
left censored observations	--- $1 - S(C_L)$	
left truncated observations	--- $f(t)/S(Y_L)$	
interval censored observations	--- $[S(L)-S(R)]$.	

When the data contain only exact or censored lifetimes, the likelihood consists of the product of four types of contributions.

$$L \propto \prod_{i \, \epsilon \, D} f(X_i) \prod_{i \, \epsilon \, R} S(C_{ri}) \prod_{i \, \epsilon \, L} (1 - S(C_{Li})) \prod_{i \, \epsilon \, I} [S(L_i) - S(R_i)], \tag{2.2}$$

where D is the set of death times, R the set of right censored observations, L the set of left censored observations, and I the set of interval censored observations.

One other censoring model is frequently invoked. When the time of right censoring, C_r, is a random variable, the censoring is called random censoring. It is usually assumed that C_r is distributed as $G(\cdot)$, independent of the lifetime X. Then $T = \min(X, C_r)$ depends both on the distribution of X and $G(\cdot)$. In terms of (T, δ), the contribution to the likelihood is

$$f(T)^\delta G(T)^\delta g(T)^{1-\delta} S(T)^{1-\delta} \tag{2.3}$$

If the censoring distribution $G(\cdot)$ is free of the regression parameters and scale parameter, the likelihood for those parameters will not depend on $G(\cdot)$.

3. ESTIMATION FOR PARAMETRIC REGRESSION MODELS

In this section, we discuss estimation of parametric models that have the accelerated failure-time feature and where the log of failure time has a linear model representation.

According to the accelerated failure-time model (1.5), with $-\theta$ in place of γ,

$$S(x \mid z) = S_0(x \exp\{\theta^t z\}) \tag{3.1}$$

where $\exp\{\theta^t z\}$ is the acceleration factor.

One consequence of this model is that the hazard rate for an individual with covariate values z is related to the baseline hazard rate by

$$h(x \mid z) = \exp\{\theta^t z\} h_0(x \exp\{\theta^t z\}) \tag{3.2}$$

where the baseline hazard rate is $h_0(\cdot) = -S_0'(\cdot) / S_0(\cdot)$.

Another consequence of the model (3.1) is that the median time to failure with covariate z is the median time to failure under baseline conditions multiplied by the acceleration factor $\exp\{\theta^t z\}$.

A second important representation of the accelerated failure time model is available. The logarithm of survival time is assumed to follow a usual linear model. From (1.4),

$$Y = \mu + \gamma^t Z + \sigma W \tag{3.3}$$

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where $\gamma^t = (\gamma_1, \dots , \gamma_p)$ is a vector of regression coefficients and W is a random variable representing the error or variation about the regression function.

The two representations (3.1) and (3.3) are closely related. If $S_0(x)$ is the survival function of the random variable $\exp(\mu + \sigma W)$, then the linear log-time model (3.3) is equivalent to the accelerated failure-time model (3.1) with $\theta = -\gamma$.

The number of useful parametric models for W is quite limited. The three most popular are the two parameter Weibull, which includes the negative exponential, the log logistic distribution, and the log normal distribution.

Under the linear model, $Y_j = \ln X_j$ and when the j-th individual has covariate vector z_j we have

$$f_j(y_j \mid z_j) = \frac{1}{\sigma} \, f_W\left(\frac{y_j - \mu - \gamma^t z_j}{\sigma}\right) \tag{3.4}$$

where $f_W(\cdot)$ is the probability density function for the error W.

The survival function, obtained by integration, is

$$S_j(y_j \mid z_j) = S_W\left(\frac{y_j - \mu - \gamma^t z_j}{\sigma}\right) \tag{3.5}$$

Similar to (2-1), the censored data likelihood is

$$L \propto \prod_{j \, \varepsilon \, D} \frac{1}{\sigma} \, f_W\left(\frac{y_j - \mu - \gamma^t z_j}{\sigma}\right) \prod_{j \, \varepsilon \, R} S_W\left(\frac{\ln C_{rj} - \mu - \gamma^t z_j}{\sigma}\right)$$

$$X \prod_{j \, \varepsilon \, L} \left(1 - S_W\left(\frac{\ln C_{Lj} - \mu - \gamma^t z_j}{\sigma}\right)\right) \tag{3.6}$$

$$X \prod_{j \, \varepsilon \, I} \left[S_W\left(\frac{\ln L_j - \mu - \gamma^t z_j}{\sigma}\right) - S_W\left(\frac{\ln R_j - \mu - \gamma^t z_j}{\sigma}\right)\right].$$

For most error distributions, maximum likelihood estimators of the model parameters based on (3.6) are found numerically. Under appropriate regularity conditions these estimators are

consistent and have an asymptotic normal distribution with a covariance matrix estimated consistently by the observed information matrix (See Borgan 1984 for details for right censored data).

3.1 Estimation with Weibull Errors

The two parameter Weibull distribution has survival function

$$S_X(x) = \exp\{-\lambda x^\alpha\}, \; x \geq 0, \; \alpha,\lambda > 0,$$

and hazard rate function

$$h_X(x) = \lambda \, \alpha x^{\alpha-1}.$$

Then, the log transform of time, $Y = \ln(X)$, has the extreme value distribution

$$S_Y(y) = \exp\{-\lambda e^{\alpha y}\}.$$

Covariates are incorporated through the linear model for the log lifetime

$$Y = \mu + \gamma^t Z + \sigma W$$

with W distributed as the standard extreme value distribution having probability density function

$$f_W(w) = \exp\{w - e^w\}, \; -\infty < w < \infty \qquad (3.7)$$

and survival function

$$S_W(w) = \exp\{-e^w\}, \; -\infty < w < \infty. \qquad (3.8)$$

This leads to a proportional hazards model for X with

$$h(x \mid z) = \lambda \, \alpha x^{\alpha-1} \exp\{\beta^t z\} \qquad (3.9)$$

where the baseline hazard, $h_0(x) = \lambda \, \alpha x^{\alpha-1}$, is the Weibull hazard rate, $\alpha = 1/\sigma$, $\lambda = \exp(-\mu/\sigma)$, and $\beta_j = -\sigma^{-1}\gamma_j$, $j=1,\ldots,p$.

Alternatively, the accelerated failure-time representation of the Weibull regression model specifies that

$$\exp\{\theta^t z\} h_0(x \exp\{\theta^t z\}) = \lambda \, \alpha x^{\alpha-1} \exp\{\alpha\theta^t z\} \qquad (3.10)$$

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is the hazard rate for an individual with covariate vector z using the baseline hazard $\lambda \alpha x^{\alpha-1}$.

Comparing (3.9) and (3.10), we see the two are the same when $\theta = \beta/\alpha = -\gamma$. The Weibull distribution is the only continuous distribution that produces both a proportional hazards model and an accelerated failure-time model.

The estimates of the parameters in the Weibull regression model must be obtained numerically. The estimates and their estimated covariance matrix, based on the log linear model (3.6), are obtained by most statistical packages.

By the invariance of maximum likelihood estimators, these can be converted to the maximum likelihood estimates

$$\hat{\beta} = -\hat{\gamma}\hat{\sigma}^{-1}, \quad \hat{\alpha} = 1/\hat{\sigma}, \quad \text{and} \quad \hat{\lambda} = \exp\{-\hat{\mu}/\hat{\sigma}\}. \tag{3.11}$$

Using the delta method, the variances and covariances can be expressed in terms of the covariance matrix of the estimators for the log linear model.

$$\text{Cov}[\hat{\beta}_j, \hat{\beta}_k] = \frac{\text{Cov}[\hat{\gamma}_j,\hat{\gamma}_k]}{\hat{\sigma}^2} - \frac{\hat{\gamma}_j\text{Cov}[\hat{\gamma}_j,\hat{\sigma}]}{\hat{\sigma}^3} - \frac{\hat{\gamma}_k\text{Cov}[\hat{\gamma}_k,\hat{\sigma}]}{\hat{\sigma}^3}$$
$$+ \frac{\hat{\gamma}_j\,\hat{\gamma}_k\,\text{Var}[\hat{\sigma}]}{\hat{\sigma}^4}, \quad j,k=1,\ldots,p; \tag{3.12}$$

$$\text{Var}[\hat{\lambda}] = \exp\{-2\frac{\hat{\mu}}{\hat{\sigma}}\}\left\{\frac{\text{Var}[\hat{\mu}]}{\hat{\sigma}^2} - 2\frac{\hat{\mu}\,\text{Cov}[\hat{\mu},\hat{\sigma}]}{\hat{\sigma}^3} + \frac{\hat{\mu}^2\,\text{Var}[\hat{\sigma}]}{\hat{\sigma}^4}\right\} \tag{13.13}$$

$$\text{Var}[\hat{\alpha}] = \frac{\text{Var}[\hat{\sigma}]}{\hat{\sigma}^4} \tag{13.14}$$

$$\text{Cov}[\hat{\beta}_j, \hat{\lambda}] = \exp\{-\frac{\hat{\mu}}{\hat{\sigma}}\}\left\{\frac{\text{Cov}[\hat{\gamma}_j,\hat{\mu}]}{\hat{\sigma}^2} - \frac{\hat{\gamma}_j\text{Cov}[\hat{\gamma}_j,\hat{\sigma}]}{\hat{\sigma}^3}\right.$$
$$\left. - \frac{\hat{\mu}\,\text{Cov}[\hat{\mu},\hat{\sigma}]}{\hat{\sigma}^3} + \frac{\hat{\gamma}_j\,\hat{\mu}\,\text{Var}[\hat{\sigma}]}{\hat{\sigma}^4}\right\}, \quad j=1,\ldots,p; \tag{13.15}$$

$$\text{Cov}[\hat{\beta}_j,\hat{\alpha}] = \frac{\text{Cov}[\hat{\gamma}_j,\hat{\sigma}]}{\hat{\sigma}^3} - \frac{\hat{\gamma}_j\,\text{Var}[\hat{\sigma}]}{\hat{\sigma}^4}\} \quad j=1,\ldots,p; \tag{13.16}$$

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$$Cov[\hat{\lambda},\hat{\alpha}] = \exp\{-\frac{\hat{\mu}}{\hat{\sigma}}\}\{\frac{Cov[\hat{\mu},\hat{\sigma}]}{\hat{\sigma}^3} - \frac{\hat{\mu}\;Var[\hat{\sigma}]}{\hat{\sigma}^4}\}. \qquad (13.17)$$

SAS, S-Plus, and BMDP provide maximum likelihood estimates of μ, σ and γ and allow for right-, left-, or interval censored data.

3.2 Estimation with Log Logistic Errors

Recall that the log logistic distribution has survival function

$$S_X(x) = \frac{1}{1+\lambda\;x^\alpha}. \qquad (3.18)$$

Its hazard rate is not monotone but first increases and then decreases.

The log of failure time $Y = \ln(X)$ has the logistic survival function

$$S_Y(x) = \frac{1}{1+\lambda\;\exp^{\alpha y}} \qquad (3.19)$$

Three equivalent models can be used to include covariates. Consider first the linear model for log time where

$$Y = \mu + \gamma^t Z + \sigma W$$

with W distributed as the standard logistic distribution having probability density function

$$f_W(w) = \frac{e^w}{(1+e^w)^2} \qquad (3.20)$$

The second representation of the log logistic is as the accelerated failure-time model (3.1) with a log logistic baseline survival function.

The third representation is obtained by replacing λ in (3.18) by $\lambda\;\exp\{\beta^t z\}$. The conditional survival function of the time to failure is then

$$S_X(x|z) = \frac{1}{1+\lambda \exp\{\beta^t z\} x^\alpha} \tag{3.21}$$

Again, as with the Weibull model, these latter parameters are related to those of the log linear model by

$$\hat{\beta} = -\hat{\gamma}\hat{\sigma}^{-1}, \ \hat{\alpha} = 1/\hat{\sigma}, \text{ and } \hat{\lambda} = \exp\{-\hat{\mu}/\hat{\sigma}\}. \tag{3.22}$$

The maximum likelihood estimates of β, λ, and α and their estimated covariance matrix can be obtained from the maximum likelihood results for μ, σ, and γ in the log linear model. The same covariance relations (3.12) - (3.17) pertain.

The factor $\exp\{-\beta^t z\}$ has a nice interpretation in this model. Consider the odds for survival beyond time x

$$\frac{S_X(x|z)}{1-S_X(x|z)} = \frac{1}{\lambda \exp\{\beta^t z\}x^\alpha} = \exp\{-\beta^t z\} \frac{S_X(x|z=0)}{1-S_X(x|z=0)} \tag{3.24}$$

We see that $\exp\{-\beta^t z\}$ is just the relative odds of survival for an individual with covariates **z** compared to an individual having the baseline characteristics **z = 0**.

The log logistic model is the only parametric model that has both a proportional odds model and an accelerated failure-time representation.

SAS, S-Plus, and BMDP provide maximum likelihood estimates of μ, σ and γ and allow for right-, left-, or interval censored data.

3.3 Estimation with Other Error Distributions.

Another choice for the distribution of W is the log normal distribution. The logarithm of the time to failure then follows the classical linear model

$$Y = \mu + \gamma^t Z + \sigma W$$

with W distributed as the standard normal distribution having probability density function

The conditional survival function is

$$S_X(x | z) = 1 - \Phi[(\ln x - \mu - \gamma^t z)/\sigma]$$

where $\Phi(\cdot)$ is the standard normal cumulative distribution function.

The general shape of the hazard rate is similar to that of the log logistic distribution. Typically, the regression models based on the normal errors are quite close to the models based on the log logistic distribution.

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One further distribution, the generalized gamma, should also be mentioned. It includes the exponential and Weibull distributions as special cases and the log normal is a limiting case.

$$f(w) = \frac{|\phi|\{\exp[\phi w]/\phi^2\}^{(1/\phi^2)}\exp\{-\exp\{\phi w\}/\phi^2\}}{\Gamma[1/\phi^2]}, \quad -\infty < w < \infty. \quad (3.25)$$

When ϕ is equal to one this model reduces to the Weibull regression model and when ϕ is equal to 0 it reduces to the log normal distribution. When $\phi=1$ and $\sigma=1$ in (3.25), then this reduces to the exponential regression model. The generalized gamma distribution is rarely used as a final model but rather serves to help choose between the Weibull and log normal models.

SAS provides maximum likelihood estimates for the log normal and the generalized gamma model. It allows for right-, left-, or interval censored data.

3.4 Diagnostics.

If a parametric model fits the data, it usually provides more precise estimates of the parameter of interest than can be obtained by nonparametric or semi-parametric methods. However, poorly fitting parametric models can yield misleading estimates. How do we check a parametric regression model? Graphical checks are preferred because tests of fit have low power for small samples and they almost always reject for large samples. The graphical techniques help identify models that are inappropriate. Often, we are left with a few different models that fit reasonably well.

The key to obtaining a graphical diagnostic procedure is the, conditional, cumulative hazard rate

$$H(x|z) = \int_0^x h(u|\,z)\,du. \quad (3.26)$$

If X has a cumulative hazard rate $H(\cdot)$ then the random variable $H(X)$ has a unit exponential distribution, since by (1.3), $P[H(X)>w] = P[X>H^{-1}(w)] = \exp\{-H[H^{-1}(w)]\} = \exp\{-e\}$.

Diagnostic plots are based on residuals. The Cox-Snell residuals are defined as

$$r_j = \hat{H}(t_j\,|\,z_j) \quad (3.27)$$

where the j-th individual has on study time t_j and covariate vector z_j. Here $\hat{H}(t_j\,|\,z_j)$ is the cumulative hazard for the fitted parametric model.

If the underlying parametric model is essentially correct, the residuals r_j should follow a standard exponential distribution. For the parametric regression models discussed in this Section, the Cox-Snell residuals are

Exponential $\qquad r_i = t_i \exp\{\hat{\beta}^t Z_i\}$ $\qquad\qquad\qquad$ (3.28)

Weibull $\qquad \exp\{\hat{\beta}^t Z_i\}\, t_i^{\hat{\alpha}}$ $\qquad\qquad\qquad$ (3.29)

Log logistic $\qquad \ln\left[\dfrac{1}{1+\exp\{\hat{\beta}^t Z_i\}\, t_i^{\hat{\alpha}}}\right]$ $\qquad\qquad$ (3.30)

and

Log normal $\qquad \ln\left\{1-\Phi\left[\dfrac{\ln[t_i]-\hat{\mu}-\hat{\gamma}^t Z_i}{\hat{\sigma}}\right]\right\}.$ $\qquad$ (3.31)

The primary diagnostic plot is a plot of the residuals from the parametric fit, r_j, versus the nonparametric Nelson-Aalen estimator of the cumulative hazard of the r_j's. This should result in a straight line pattern having slope 1, if the parametric model is reasonable.

An alternative, but equivalent approach, is based on the log time linear model representation (3.3). Analogous to the classical normal linear model theory, standardized residuals

$$s_j = \frac{\ln[t_i]-\hat{\mu}-\hat{\gamma}^t Z_i}{\hat{\sigma}} \qquad\qquad\qquad (3.32)$$

can be defined. Under the log normal model, these residuals approximate a, possibly censored, random sample from a standard normal distribution. If the Weibull model holds, the standardized residuals should behave like a censored sample from the standard extreme value distribution (3.7). Under the log logistic model (3.18), the standardized residuals are nearly a censored sample from the standard logistic distribution (3.21). The hazard plots obtained from this approach are exactly the same as those obtained by the exponential hazard plot for the Cox-Snell residuals.

3.5 Example

To illustrate these procedures we consider a sample of 877 women diagnosed with an initial infection of either gonorrhea or chlamydia. While both of these disease are treated quite easily it remains a mystery why the re infection rate remains high for these diseases in some sub-populations. To study risk factors for re infection, patients were followed until they had a re infection or until the

closing date of the study. During the study period 347 (40%), of the women experienced a re infection. The follow-up time on the 877 women ranged from 1 to 1,529 days with a median of 247 days. In this example we have selected three of the factors considered by investigators: years of schooling (median 11.4 years with a range of 6-18 years), condom use (6% always, 58% sometimes and 34% never), and the indicator of whether the patient had oral sex within the 12 months prior to diagnosis (33%). Years of schooling is treated as a continuous covariate, while condom use is coded as two binary covariates (sometime and never use condoms). A complete data set can be found at www.biostat.mcw.edu:80/klein/std.html.

Using the SAS@ procedure LIFEREG we fit the Weibull, log logistic and log normal regression models to this data. Using the linear models formulation $Y = \mu + \gamma'Z + \sigma W$, the estimates and standard errors of γ and σ are in Table 1.

Table 1
Maximum Likelihood Estimators Based On The Linear Models Formulation

Effect	Weibull $\hat{\gamma}$	SE	p	Log Logistic $\hat{\gamma}$	SE	p	Log Normal $\hat{\gamma}$	SE	p
Intercept	4.786	0.571	<.0001	4.067	0.643	<.0001	3.786	0.694	<.0001
Z_1: Years of School	0.163	0.044	.0002	0.171	0.048	.0004	0.186	0.053	.0004
Z_2: Oral sex	0.613	0.172	.0003	0.618	0.183	.0008	0.627	0.196	.0014
Z_3: Sometime use Condom	0.066	0.300	.8252	0.232	0.355	.5147	0.386	0.364	.2892
Z_4: Never use Condom	0.393	0.310	.2048	0.587	0.365	.1080	0.760	0.376	.0432
σ	1.304	0.058		1.112	0.050		2.085	0.083	
Log Likelihood	-976.44			-982.47			-991.33		

While the models presented in Table 1 are not nested, the value of the maximum likelihood provides a means of selecting the best fitting parametric model. Here the Weibull model appears to fit the data the best. Using this model one can compute the estimates of λ, β, and α using (3.11)-(3.17). The estimates and their standard errors are given in the following table.

Table 2
Estimates based on the Weibull model

Parameter	Estimate	Stand. Err
λ	0.02549	0.01221
Z_1: Years of School	-0.12561	0.03375
Z_2: Oral sex	-0.47008	0.13001
Z_3: Sometime use Condom	-0.05074	0.22963
Z_4: Never use Condom	-0.30109	0.23721
α	0.76660	0.03421

Note that the model suggests that patients who had fewer years of schooling and who had oral sex in the last year tend to re infected later and that condom use is not related to the re infection rate.

Figure 1 shows the Cox-Snell residual plots for the three parametric models. The curves, which all should be equal to the 45° line, all suggest that the models fitted here are plausible. Again, the Weibull plot seems to be closest to the 45° line.

4. Semi-Parametric Regression Models

In this Section we shall discuss the estimation of regression parameters for the multiplicative hazards regression model. For this model, most commonly called the proportional hazards model or the Cox model, the conditional hazard rate of X given $z(x)$ is given by

$$h(x|z) = h_0(x) \exp\{\beta^t z(x)\},$$ (4.1)

where $z(x)$ is a p-vector of possibly time dependent covariates, β is a p-vector of regression coefficients and $h_0(x)$ is a baseline hazard rate. In most applications of this model the main interest is on the estimation of the regression coefficients and thus the baseline hazard rate $h_0(\cdot)$ is left unspecified.

Estimation for the Cox model is based on a partial likelihood rather than a full likelihood. For right censored and left truncated data Andersen et al (1993) have shown that in most cases the large sample properties of maximum partial likelihood estimates are similar to the usual properties of a maximum likelihood estimator based on the complete likelihood. That is the maximum partial likelihood estimators of β are consistent and asymptotically normal with a covariance estimated consistently by the inverse of the observed information.

4.1 Partial Likelihoods

To estimate the risk coefficients, β, we need a partial likelihood function. For simplicity we shall assume we have only right censored data, $(t_j, \delta_j, \{Z_j(t), 0 \leq t \leq t_j\})$, $j=1,...,n$, where t_j is the time on study for the j-th patient, δ_j is the event indicator for the j-th patient ($\delta_j=1$ if event has occurred, 0 if the lifetime is right censored) and $Z_j(t)= (Z_{j1}(t),...,Z_{jp}(t))^\tau$ is the vector of covariates for the j-th individual at time t. For the covariate process we assume that the values of $Z_j(t)$ are known for any time point at which the subject is under observation. We assume that censoring is non informative in that, given $Z_j(t)$, the event and censoring time for the j-th patient are independent. We first assume that all the event times are distinct. Let $T_1 < T_2 < \cdots < T_D$ denotes the ordered event times, $Z_{(j)}(T_j)$ is the covariate associated with the individual whose failure time is T_j and $R(T_j)$ is the risk set at time T_j (that is $R(T_j)$ is the set of all individuals who were still under study at a time just prior to t_j). The partial likelihood function is

$$L(\beta) = \prod_{i=1}^{D} \frac{\exp\{\beta^t z_{(i)}(T_i)\}}{\sum\limits_{j \in R(T_i)} \exp\{\beta^t z_j(T_i)\}} \tag{4.2}$$

This is treated as a usual likelihood and inference is carried out by usual means. It is of interest to note that the numerator of the likelihood depends only upon information from the individual who experiences the event, whereas the denominator utilizes information on all individuals who have not yet experienced the event (including some individuals who will be censored later).

When there is more than one death at a given time several partial likelihoods have been proposed. Again let $T_1 < T_2 < ... < T_D$ denote the D distinct ordered event times. At time T_i let d_i be the number of deaths, $\mathbb{D}_i$ be the set of individuals who die, $s_i = \sum\limits_{j \in \mathbb{D}_i} z_j(T_i)$, and $R(T_i)$ be the risk set at time T_i

The first partial likelihood is due to Breslow (1974) and is the default partial likelihood in most statistical packages. Here

$$L_1(\beta) = \prod_{i=1}^{D} \frac{\exp\{\beta^t s_i\}}{[\sum\limits_{j \in R(T_i)} \exp\{\beta^t z_j(T_i)\}]^{d_i}}. \tag{4.3}$$

Efron (1977) suggests a partial likelihood of

$$L_2(\beta) = \prod_{i=1}^{D} \frac{\exp\{\beta^t s_i\}}{\prod_{j=1}^{d_i} \left[\sum_{k \in R(T_i)} \exp\{\beta^t Z_k(T_i)\} - \frac{j-1}{d_i} \sum_{k \in \mathbf{D}_i} \exp\{\beta^t Z_k(T_i)\} \right]} . \qquad (4.4)$$

When the number of ties are small, Efron's and Breslow's likelihoods are quite close.

The third partial likelihood, due to Cox(1972), is based on a discrete time hazard rate model. If we let $h(t|Z)$ denote the conditional probability of death in the interval $(t, t+1)$ given survival to the start of the interval and if we assume

$$\frac{h(t|\mathbf{Z})}{1 - h(t|\mathbf{Z})} = \frac{h_0(t)}{1 - h_0(t)} \exp\{\beta^t z(t)\}$$

then this likelihood is the proper partial likelihood. To construct the likelihood, let Q_i denote the set of all subsets of d_i individuals who could be selected from the risk set $R(T_i)$. Each element of Q_i is a d_i-tuple of individuals who could have been one of the d_i failures at time T_i. Let $q = (q_1, ..., q_{d_i})$ be one of these elements of Q_i and define $s_q^* = \sum_{j=1}^{d_j} z_{q_j}(T_i)$. Then the discrete partial likelihood is

$$L_3(\beta) = \prod_{i=1}^{D} \frac{\exp\{\beta^t s_i\}}{\sum_{q \in Q_i} \exp\{\beta^t s_q^*\}} . \qquad (4.5)$$

When there are no ties between the event times all these likelihoods reduce to the likelihood (4.2).

The partial likelihoods (4.2)-(4-5) can be extended in a natural way to allow for left truncated or delayed entry data. To do this one needs to redefine the risk set to be the set of all individuals under observation at time t with an entry time into the study less than t who are still alive or are dead at time t.

4.3 Inference for β

Inference for the regression coefficients, β, is based on the partial likelihood. For ease of exposition we shall restrict our discussion to the case of right censored data with distinct death times and fixed time covariates. In this case from (4.2) we see that the log likelihood is

$$LL(\beta)= \sum_{i=1}^{D} \sum_{k=1}^{p} \beta_k Z_{(i)k} - \sum_{i=1}^{D} \ln\Big[\sum_{j\in R(T_i)} \exp\{\beta^t z_j\}\Big] \qquad (4.6)$$

The partial maximum likelihood (pmle) estimates are found by maximizing (4.2), or equivalently, (4.6).   The efficient score equations are found by taking partial derivatives of (4.6) with respect to the β's as follows. Let $U_h(\beta) = \partial LL(\beta)/\partial \beta_h$, $h=1,...,p$. That is,

$$U_h(\beta)= \sum_{i=1}^{D} Z_{(i)h} - \sum_{i=1}^{D} \frac{\displaystyle\sum_{j\in R(t_i)} Z_{jh} \exp\{\beta^t z_j\}}{\displaystyle\sum_{j\in R(t_i)} \exp\{\beta^t z_j\}}. \qquad (4.7)$$

The information matrix is the negative of the matrix of second derivatives of the log likelihood and is given by $I(\beta)=(I_{gh}(\beta))_{pxp}$ with the (g,h)th element given by

$$I_{gh}(\beta)= \sum_{i=1}^{D} \frac{\displaystyle\sum_{j\in R(T_i)} Z_{jg}Z_{jh}\exp\{\beta^t z_j\}}{\displaystyle\sum_{j\in R(T_i)} \exp\{\beta^t z_j\}} - \sum_{i=1}^{D} \Big\{\frac{\displaystyle\sum_{j\in R(T_i)} Z_{jg}\exp\{\beta^t z_j\}}{\displaystyle\sum_{j\in R(T_i)} \exp\{\beta^t z_j\}}\Big\} \Big\{\frac{\displaystyle\sum_{j\in R(T_i)} Z_{jh}\exp\{\beta^t z_j\}}{\displaystyle\sum_{j\in R(T_i)} \exp\{\beta^t z_j\}}\Big\}. \qquad (4.8)$$

For large samples there are three test statistics that are commonly used to test the global hypothesis that $\beta = \beta_0$. The first test is based on the asymptotic normality of the pmle. Let **b** denote the pmle's, then for large samples **b** has a p-variate normal distribution with mean β and variance-covariance estimated consistently by $I^{-1}(\mathbf{b})$. The test statistic is

$$X_W^2 =(\mathbf{b}-\beta_0)^t I(\mathbf{b})(\mathbf{b}-\beta_0), \qquad (4.9)$$

which has a limiting chi-squared distribution with p degrees of freedom when $\beta = \beta_0$.

The second test is the likelihood ratio test with test statistic

$$X_{LR}^2 = 2\{LL(\mathbf{b})-LL(\beta_o)\}, \qquad (4.10)$$

which also has a limiting chi-squared distribution with p degrees of freedom when $\beta = \beta_0$.

The third test is based on the limiting distribution of the efficient score vector $\mathbf{U}$. For large samples, $\mathbf{U}(\beta)$ is asymptotically p-variate normal with mean $\mathbf{0}$ and covariance $\mathbf{I}(\beta)$. The test statistic is

$$X^2_{SC}=\mathbf{U}(\beta_o)^t\mathbf{I}^{-1}(\beta_o)\ \mathbf{U}(\beta_o) \tag{4.11}$$

which has a large sample chi-squared distribution with p degrees of freedom when $\beta = \beta_0$.

Wald, likelihood ratio and score tests can also be used to test local hypotheses about subsets of β. Let $\beta = (\beta_1{}^t,\beta_2{}^t)^t$, where β_1 is a qx1 vector of the β's of interest and β_2 is the vector of the remaining p-q β's. We wish to test the hypothesis that $\beta_1=\beta_{10}$. To construct the Wald test we partition the information matrix as

$$\mathbf{I}= \begin{pmatrix} \mathbf{I}_{11} & \mathbf{I}_{12} \\ \mathbf{I}_{21} & \mathbf{I}_{22} \end{pmatrix},$$

where $\mathbf{I}_{11}$ ($\mathbf{I}_{22}$) is the qxq ((p-q)x(p-q)) sub matrix of second partial derivatives of the minus the log likelihood with respect to β_1 (β_2) and $\mathbf{I}_{12}$ and $\mathbf{I}_{21}$ the matrices of mixed second partial derivatives. The Wald test statistic is

$$X^2_W =(\mathbf{b}_1-\beta_{10})^t\ (\mathbf{I}^{11}(\mathbf{b}))^{-1}\ (\mathbf{b}_1-\beta_{10}) \tag{4.12}$$

where $\mathbf{I}^{11}(\mathbf{b})$ is the upper qxq sub matrix of $\mathbf{I}^{-1}(\mathbf{b})$.

For the other two tests, we let $\mathbf{b}_2(\beta_{10})$ be the pmle of β_2 based on the log likelihood with the first q β's fixed at a value β_{10}. The likelihood ratio statistic is

$$X^2_{LR} = 2\{LL(\mathbf{b})-LL[\beta_{10},\mathbf{b}_2(\beta_{10})]\}. \tag{4.13}$$

For the score tests let $\mathbf{U}_1\ [\beta_{10},\mathbf{b}_2(\beta_{10})]$ be the qx1 vector of scores for β_1 evaluated at the hypothesized value of β_1 and at the restricted pmle for β_2. Then

$$X^2_{SC}=\mathbf{U}_1\ [\beta_{10},\mathbf{b}_2(\beta_{10})]^t\ [\mathbf{I}^{11}(\beta_{10},\mathbf{b}_2(\beta_{10}))]\ \mathbf{U}_1[\beta_{10},\mathbf{b}_2(\beta_{10})]. \tag{4.14}$$

For large samples all three statistics have a limiting chi-square distribution with q degrees of freedom when $\beta_1 = \beta_{10}$.

Most major statistics packages provide point estimates and both global and local tests for right censored data. SAS, BMDP and SPlus also allow for left truncated data.

4.4 Estimation of the Survival function

Once the pmle's of β, are obtained the baseline cumulative hazard rate and the baseline survival function can be estimated. These estimates are only appropriate when all the covariates are fixed at time 0. The most common estimator is Breslow's (1974) estimator. Let $\mathbf{b}$, be the pmle of β and $\hat{V}(\mathbf{b})$, be the estimated covariance matrix of $\mathbf{b}$, obtained from the inverse of the information matrix. Let $T_1 < T_2 < ... < T_D$ denote the distinct death times and d_i be the number of deaths at time T_i. Define

$$W(T_i; \mathbf{b}) = \sum_{j \in R(T_i)} \exp\{\mathbf{b}^t \mathbf{z}_j\} . \qquad (4.15)$$

The estimate of the baseline cumulative hazard rate, $H_0(t) = \int_0^t h_0(u)du$ is

$$\hat{H}_0(t) = \sum_{T_I \le t} \frac{d_i}{W(T_i; \mathbf{b})}, \qquad (4..16)$$

which is a step function with jumps at the observed death times. The estimator of the baseline survival function, $S_0(t) = \exp\{- H_0(t)\}$, is given by

$$\hat{S}_0(t) = \exp\{-\hat{H}_0(t)\} . \qquad (4.17)$$

This is an estimator of the survival function of an individual with a baseline set of covariate values, $\mathbf{z} = \mathbf{0}$. To estimate the survival function for an individual with a covariate vector $\mathbf{z} = \mathbf{z}_0$, we use the estimator

$$\hat{S}(t \mid Z = \mathbf{z}_0) = \hat{S}_0(t)^{\exp(\mathbf{b}^t \mathbf{z}_0)} \qquad (4.18)$$

Under rather mild regularity conditions (See Andersen et al (1993)) this estimator, for fixed t, has an asymptotic normal distribution with mean $S(t \mid Z = \mathbf{z}_0)$ and a variance which can be estimated by

$$\hat{V}[\hat{S}(t \mid Z = \mathbf{z}_0)] = [\hat{S}(t \mid Z = \mathbf{z}_0)]^2 \{Q_1(t) + Q_2(t; \mathbf{z}_0)\}, \qquad (4.19)$$

where

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$$Q_1(t) = \sum_{T_i \le t} \frac{d_i}{W(T_i, b)^2} \tag{4.19}$$

which is an estimator of the variance of $\hat{H}_0(t)$ if $\mathbf{b}$ were the true value of β. The term

$$Q_2(t ; \mathbf{Z_0}) = Q_3(t ; \mathbf{Z_0})^t \hat{V}(\mathbf{b}) \; Q_3(t ; \mathbf{Z_0}) \tag{4.20}$$

with Q_3 the p-vector whose k-th element is defined by

$$Q_3(t, \mathbf{Z_0})_k = \sum_{T_i \le t} \left[\frac{W^{(k)}(T_i; \mathbf{b})}{W(T_i; \mathbf{b})} - Z_{0k} \right] \left[\frac{d_i}{W(T_i, \mathbf{b})} \right], \quad k=1, ..., p \tag{4.21}$$

where

$$W^{(k)}(T_I; \mathbf{b}) = \sum_{j \in R(T_i)} Z_{jk} \exp(\mathbf{b}^t Z_j),$$

reflects the uncertainty in estimation processes added by estimation of β.

SAS, BMDP and SPlus have routines which provide estimates of the survival function following a Cox regression analysis.

4.5 Stratified Proportional Hazards Models

In some instances the proportionality assumption in the Cox model does not hold for some covariate. In this case it is possible to fit a proportional hazards model with a distinct baseline hazard rate for each level of the covariate. Suppose the covariate has s levels or strata and suppose that for the j-th level the baseline hazard rate is $h_{0j}(t)$. The stratified proportional hazards model is

$$h_j(t \mid Z(t)) = h_{0j}(t) \exp\{\beta^t Z(t)\}, \; j = 1,...,s. \tag{4.22}$$

Here the regression coefficients are assumed to act in a similar manner in each of the stratum.

Estimation and hypothesis testing methods follow as before where the partial log likelihood function is

$$LL(\beta) = \{LL_1(\beta)\} + \{LL_2(\beta)\} + ... + \{LL_s(\beta)\}, \tag{4.23}$$

where $LL_j(\beta)$ is the log partial likelihood using only the data for those individuals in the j-th stratum.

4.5 Diagnostics

A number of diagnostic tests and plots have been suggested for the proportional hazards model. In this section we shall review a few of these techniques. Other techniques can be found in Chapter 11 of Klein and Moeschberger (1997).

We shall first look at methods for checking the proportional hazards assumption for a given covariate. A common approach to checking this assumption for a fixed covariate z_1 is to create an artificial time dependent covariate, $z_2(t)$, defined as $z_2(t) = z_1 \times g(t)$ for some known function of t (typically log[t]). Here the model for the conditional hazard rate is

$$h(t \mid z_1) = h_0(t) \, \exp\{\beta_1 z_1 + \beta_2 [z_1 \times g(t)]\}$$

which reduces to the proportional hazards model when β_2 is equal to zero.

Several graphical checks are available to check for proportional hazards. Consider checking for proportional hazards for a discrete covariate z_1 after adjustment for other covariates, z_2. One technique is to fit a proportional hazards model to z_2, stratified on z_1. That is, we fit the model

$$h(t \mid z_1 = j, z_2) = h_{0j}(t) \, \exp\{\beta_2^t z_2\}.$$

If the model has proportional hazards for z_1 then we must have $h_{0j}(t) = h_0(t) e^{b_1 z_1}$, so that the cumulative baseline hazard rates for each level of z_1 are constant multiples of each other or equivalently the logs of the cumulative baseline hazard rates are parallel. Let $\hat{H}_{0j}(t)$ be the estimated baseline hazard rate (4.16). If the proportionality assumption holds then a plot of $\ln[\hat{H}_{01}(t)]$, ... , $\ln[\hat{H}_{0K}(t)]$ versus t should yield parallel lines. An alternative is to plot $\ln[\hat{H}_{0j}(t)] - \ln[\hat{H}_{01}(t)]$, j=2,...,K versus t which should yield a series of constant curves. Andersen (1982) suggests a plot of $\hat{H}_{0j}$, j=2, ..., K versus $\hat{H}_{01}$ for all t. If proportionality holds these should be straight lines. If $H_{0j}(t) = \exp(\gamma_j) H_{01}(t)$ then the slope of these lines is a crude estimate of γ_g. Gill and Schumacher (1987) have shown that if the plot of $\hat{H}_{0j}(t)$ versus $\hat{H}_{01}(t)$ is a convex (concave) function then the ratio $h_{0j}(t)/h_{01}(t)$ is an increasing (decreasing) function of t. If the plot is piecewise linear then this ratio is piecewise constant. All three plots should be interpreted with some care since the variances of the curves are not constant over time.

If the proportional hazards assumption is valid then the martingale residual can be used to check the appropriate form of the regression function. To define this residual we let $z_j(t)$ denote the covariate vector for the j-th individual. Let $N_j(t)$ be a counting process with the value 1 if at time t the t_j-th individual is dead and 0 if they are alive. Define $Y_j(t)$ as the indicator that person j is under study at time t. Finally, let b and $\hat{H}_0(\cdot)$ be the pmle of β and $H_0(\cdot)$, respectively. The martingale residual for the j-th observation is

$$\hat{M}_j = N_j(\infty) - \int_0^\infty Y_j(t) \exp\{b^t Z_j(t)\} d\hat{H}_0(t), \quad j=1,\dots,n. \tag{4.24}$$

The residuals have the properties that they sum to zero and for large samples behave like an uncorrelated sample from a population with a zero mean. If the true values of β and $H_0(\cdot)$ were used in (4.24) then the functions M_j would be martingales. The residuals can be interpreted as the difference over time of the observed number of events minus the expected number of events under the assumed Cox model.

Martingale residuals are most commonly used to determine the best functional form for a given covariate assuming the model is known for the remaining covariates. Suppose $z = (z_1, z_2)$ with a Cox model assumed for z_2. The model is

$$h(t \mid z_1, z_2) = h_0(t) \exp\{\beta_2^t z_2 + f(z_1)\}$$

with $f(\cdot)$ to be determined form the data. To find $f(\cdot)$ we fit a Cox model using z_2 and compute the martingale residuals. A plot of $(z_j, \hat{M}_j)$ is made and a smooth (Cleveland (1979)) is fit to the scatter diagram. The smoothed curve is the suggested form of $f(\cdot)$. For example, if the smooth is linear then no transformation of z_1 is needed while if the curve has a threshold then a discretized version of the covariate is used. A detailed derivation of these results is found in Fleming and Harrington (1991) or Therneau et al (1990).

The martingale residuals can also be used to check for outliers, but since the residuals lie in the interval $(-\infty, 1)$ they tend to be highly skewed. A residual which tends to have a more normal shape is the deviance residual, defined by

$$D_j = \text{sgn}[\hat{M}_j]\{-2[\hat{M}_j + \delta_j \log(\delta_j - \hat{M}_j)]\}^{1/2} \tag{4.25}$$

This residual has a value of 0 when $\hat{M}_j$ is zero. The logarithm tends to inflate the value of the residual when $\hat{M}_j$ is close to 1 and shrink large negative values of $\hat{M}_j$. To check for outliers we plot D_j versus $b^t z_j$. When there is light to moderate censoring the D_j should look like a sample of normally distributed noise. When there is heavy censoring a large collection of points near zero will distort the normal approximation. In either case potential outliers will have deviance residuals which are too large in absolute value.

While the deviance residual is useful for checking for outliers in a data set, the score residuals, are used for checking the influence an observation has on the estimate of β. The score residual is defined for the j-th observation and the k-th covariate as

$$S_{jk} = \delta_i\{Z_{jk} - \bar{Z}_k(t_j)\} - \sum_{h=1}^{n} \{Z_{jk} - \bar{Z}_k(t_h)\}\exp\{\mathbf{b^t Z_j}\}d\hat{H}_0(t_h), \qquad (4.26)$$

for $j=1,...,n$ and $k=1,...,p$. Here

$$\bar{Z}_k(t) = \frac{\sum_{j=1}^{n} Y_j(t) Z_{jk}(t)\exp\{\mathbf{b^t Z_j}(t)\}}{\sum_{j=1}^{n} Y_j(t) \exp\{\mathbf{b^t Z_j}(t)\}}$$

and $d\hat{H}_0(t_h)$ is the size of the jump in $\hat{H}_0(\cdot)$ at t_h. The first term $\delta_i\{Z_{jk} - \bar{Z}_k(T_j)\}$ is the partial residual of Schoenfeld (1982) and is the difference between the covariate Z_{jk} at the failure time and the expected value of the covariate at this point in time.

The standardized score residual vector, $\Delta = \mathbf{I(b)}^{-1}(S_{j1},...,S_{jp})^t$, is an approximation of the difference in the pmle of β based on the complete data and the pmle of β based on a data set with the j-th observation removed. Plots of these standardized residuals versus the case number, the covariate or time are used to check the influence of the j-th observation on the k-th covariate.

4.6 Example

We shall continue the example discussed in Section 3.5 by analyzing the data using a proportional hazards model. To illustrate the methods we shall restrict ourselves to those methods available in SAS. As a first step in the analysis we fit a Cox model to the five covariates z_1: Years of Schooling, z_2: Oral sex in last year (1-yes, 0-no), z_3: Occasional Condom use (1-Sometime use, 0-always or never) and z_4: No condom use (1-never use condom, 0- Sometime of always). The ANOVA table for this model is

Table 3
PMLE For The Simple Cox Model

	Estimate	SE	Chi-Square	p
β_1 Schooling	-0.127	0.338	14.13	0.002
β_2 Oral Sex	-0.465	0.120	12.79	0.003
β_3 Sometime Use Condom	-0.042	0.230	0.03	.8556
β_4 Never use Condom	-0.309	0.237	1.69	.1933

This model gives results quite similar to those found using the parametric models.

To check for proportional hazards, we fit four time dependent covariates $z_{i+4} = z_i \ln(t)$, $i=1,...,4$. The ANOVA table for this model is

Table 4
Checking The Proportionality Assumption

	Estimate	SE	Chi-Square	p
β_1 Schooling	-0.153	0.106	2.07	0.150
β_2 Oral Sex	-0.345	0.427	0.65	0.419
β_3 Sometime Use Condom	-1.108	0.588	3.55	0.059
β_4 Never use Condom	-1.682	0.646	6.79	0.009
β_5: $Z_1 \ln(t)$	0.005	0.021	0.06	0.806
β_6: $Z_2 \ln(t)$	-0.024	0.083	0.08	0.773
β_7: $Z_3 \ln(t)$	0.229	0.124	3.39	0.065
β_8: $Z_4 \ln(t)$	0.289	0.133	4.71	0.029

This model suggests that the proportional hazards assumption is not valid for the factor representing condom use. Figures 2 and 3 confirm this observation. Figure 2 looks at the difference in log baseline hazard rates based on the models with z_1 and z_2, stratified on the three levels of condom use. Figure 3 is the Andersen plot of the cumulative hazard rate for the baseline group (always use condom) versus the other two groups. Both plots show a marked departure from what one would expect if the proportionality assumption held.

To account for the non proportionality of the condom factor we could either consider models which stratify on condom use or we could model condom use by time dependent covariates. We prefer the later approach here. We shall create four time dependent covariates for the condom use factor:

$z_9(t) = z_3 I[t \leq \tau]$ ("early" effect of occasional condom use)

$z_{10}(t) = z_4 I[t \leq \tau]$ ("early" effect of no condom use)

$z_{11}(t) = z_3 I[t > \tau]$ ("late" effect of occasional condom use)

$z_{12}(t) = z_4 I[t > \tau]$ ("late" effect of no condom use)

and fit the model z_1, z_2, $z_9(t)$,...,$z_{12}(t)$. To find τ we fit a series of models with different values of τ and pick the model which gives the largest partial likelihood. While τ can be any re infection time found in the data, our grid search was over the grid 10, 20, ..., 1000. We found the "best" value of τ to be 70 days. Using $\tau=70$ days one can check for proportional hazards for each of the time dependent covariates $z_9(t)$, ..., $z_{10}(t)$ by creating 4 additional time dependent covariates $z_{k+12}(t) = z_{8+k} \ln(t)$, k=1,...,4. In this model proportional hazards held.

Before presenting the final we model we need to check on the appropriateness of the functional form for z_1. While martingale residuals are well defined for time dependent covariates to date they are not available in SAS. In figure 4 we present the martingale residual plot and the smooth

for years of schooling based on a model using z_1 and z_2, only. The dashed curve, which appears, roughly linear suggest that no transformation of z_1 is needed in the final model. The final model is

Table 5
Final Proportional Hazards Model

	Estimate	SE	Chi-Square	p
β_1 Schooling	-0.128	0.034	14.33	0.0002
β_2 Oral Sex	-0.463	0.130	12.67	0.0004
β_9	-0.602	0.341	3.11	0.0777
β_{10}	-1.058	0.379	7.80	0.0052
β_{11}	0.287	0.313	0.83	0.3596
β_{12}	0.074	0.319	0.05	0.8155

The model suggest that frequency of condom use is related to re infection for the first 70 days after diagnosis and that after that point in time there is no effect.

Figure 5 shows a plot of the deviance residuals by year of schooling in the model with z_1 and z_2 only. If the model is correct then these residuals should look like a sample of standard normal noise at each level of schooling. Figures 6 and 7 are the standardized score residuals for years of schooling and oral sex, respectively. Figure 6 show that the following three patients have the greatest effect on the estimate of the risk coefficient:

Time To Re infection	Re infection	Years In School	Residual
4	Yes	6	-0.0052
11	Yes	17	0.0069
131	Yes	16	0.0051

Here, the last two patients are women with a long period of schooling who are re infected earlier then expected by the model. For the oral sex covariate the three most influential patients are:

Time To Re infection	Re infection	Oral Sex	Residual
1005	no	yes	-0.0156
5	yes	yes	0.0143
3	yes	yes	0.0145

Here the first patient is a woman who had not had oral sex but had a re infection time longer than expected by the model. The last two are women who had oral sex that had re infection time shorter than predicted by the model.

5. Additive Hazards Regression

The additive hazard rate model (1.11) assumes a linear regression formulation for the conditional hazard rate. The model can be formulated as follows. Let $h_i(t)$ be the hazard rate for the i-th individual and let $h(t) = (h_1(t), \ldots, h_n(t))^t$. Define the nx(p+1) matrix $Y(t)$ as follows: if the i-th individual is at risk at time t (i.e. alive and under observation just prior to t) then the i-th row of $Y(t)$ is $(1, z_{1i}, , z_{ip})^t$. Otherwise the corresponding row of $Y(t)$ is set to zero. Then

$$h(t) = Y(t)\,\beta(t), \tag{5.1}$$

where $\beta(t) = (\beta_0(t), \ldots, \beta_p(t))^t$ is a p+1 vector of regression functions.

Direct estimation of $\beta(t)$ is difficult. However, Aalen (1989), has derived least squares estimators of the cumulative regression functions,

$$B_j(t) = \int_0^t \beta_j(u)du \ , \ j=0,\ldots,p. \tag{5.2}$$

Let $T_1 < T_2 < \ldots$ be the ordered event times. Let $X(T_k)$ be any generalized inverse of $Y(t)$ and I_k be a n vector of zeros except for a one in the position for the subjects who die at T_k. The least squares estimator of $B(t)$ is

$$\hat{B}(t) = \sum_{T_k \le t} X(T_k)\,I_k. \tag{5.3}$$

In practice any generalized inverse of $Y(\cdot)$ can be used. Aalen (1989) suggest a local least squares approach with

$$X(t) = [Y(t)^t\,Y(t)]^{-1}Y(t)^t. \tag{5.4}$$

Note that $B(t)$ is estimable only as long as $Y(\cdot)$ is of full rank. Estimates of the regression coefficients, $\beta(\cdot)$ are obtained by kernel smoothing techniques discussed in Ramlau-Hansen (1983).

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The estimator (5.2) is a stochastic integral with respect to a martingale (See Aalen (1978)) so the estimator is almost unbiased (i.e. it is unbiased up to the time at which $Y(t)$ is no longer of full rank) and is asymptotically normal with an estimated covariance matrix given by

$$V(t) = \sum_{T_k \leq t} X(T_k) \, I_k^d \, X(T_k)^t. \tag{5.5}$$

where I_k^d is a diagonal matrix with I_k on the diagonal.

Aalen (1989) discusses tests of the hypothesis H_j: $\beta_j(t)=0$ which are based on the weighted integral of the estimates of $\beta_j(t)$. Here we consider a more general problem of testing if a linear combination of the β's are equal to 0. Let C be a $r \times p+1$ matrix. Consider testing the hypothesis H_0: $C \beta(t) = 0$. A test statistic for H_0 is based on the vector

$$U_c = \sum_{T_k \leq \tau} K_C(T_k) \, C \, X(T_k) I_k, \tag{5.6}$$

where $K_C(T_k)$ is an $r \times p+1$ matrix of predictable weights. While any predictable matrix can be used for the weight matrix by analogy to the ordinary least squares regression problem where the variance of $C \beta$ is proportional to $C(Y(t)^t Y(t))^{-1} C^t$ we propose using as weights:

$$K_C(t) = \{ C(Y(t)^t Y(t))^{-1} C^t \}^{-1} \tag{5.6}$$

This choice of a weight function reduces to Aalen(1989)'s "TST" test of H_j: $\beta_j(t)=0$, when C is a diagonal matrix with 1's along the main diagonal. It allows for a natural test for contrasts between regression functions.

One can show that the variance matrix for U_C is

$$V_C = \sum_{T_k \leq \tau} K_C(T_k) \, C \, X(T_k) \, I_k^d \, X(T_k)^t \, C' \, K_C(t)^t \tag{5.7}$$

and that U_C has a limiting multivariate normal distribution. The test statistic for H_0 is

$$X^2 = U_C^t \, V_C^{-1} \, U_C, \tag{5.8}$$

which has a limiting chi squared distribution with r degrees of freedom.

5.2 Example

We shall use the additive model to examine the effect of years of schooling, condom use and oral sex on the time to re infection of a sexual disease. While the additive model is not available in standard statistical packages, a SAS IML macro is available on the Medical College Of Wisconsin Division Of Biostatistics web site at www.biostat.mcw.edu (See Howell and Klein 1996 for details). This macro was used to produce the results reported here.

We fit the additive model to the factors years of schooling, oral sex in the last 12 months, and condom use (sometimes or never). The one degree of freedom tests of the hypothesis of no effect for a given covariate are:

Table 6
Anova Table For The Additive Hazards Model

Effect	Chi-square	d.f..	p-value
β_1 Schooling	15.1969	1	<0.0001
β_2 Oral Sex	16.9033	1	<0.0001
β_3 Sometime Use Condom	5.2974	1	0.0214
β_4 Never use Condom	2.7936	1	0.0946

The two degree of freedom test of the hypothesis that $\beta_3(t)=\beta_4(t)=0$ for all t based on (5.6)-(5.8), has a chi-square of 5.3641 with a p-value of 0.0684.

Figures 8-12 show the estimates of B(t) and pointwise 95% confidence intervals. The estimates are valid in the range 0 to 1482 days, after which $Y(\cdot)$ is singular. The slope of these curves gives a crude estimate of $\beta(t)$.

Acknowledgments

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Figure 1

Cox−Snell Residuals for Parametric Models

Estimated Cumulative Hazard Rates

Residual

Legend

Weibull   Log logistic   Log normal
45 degree line
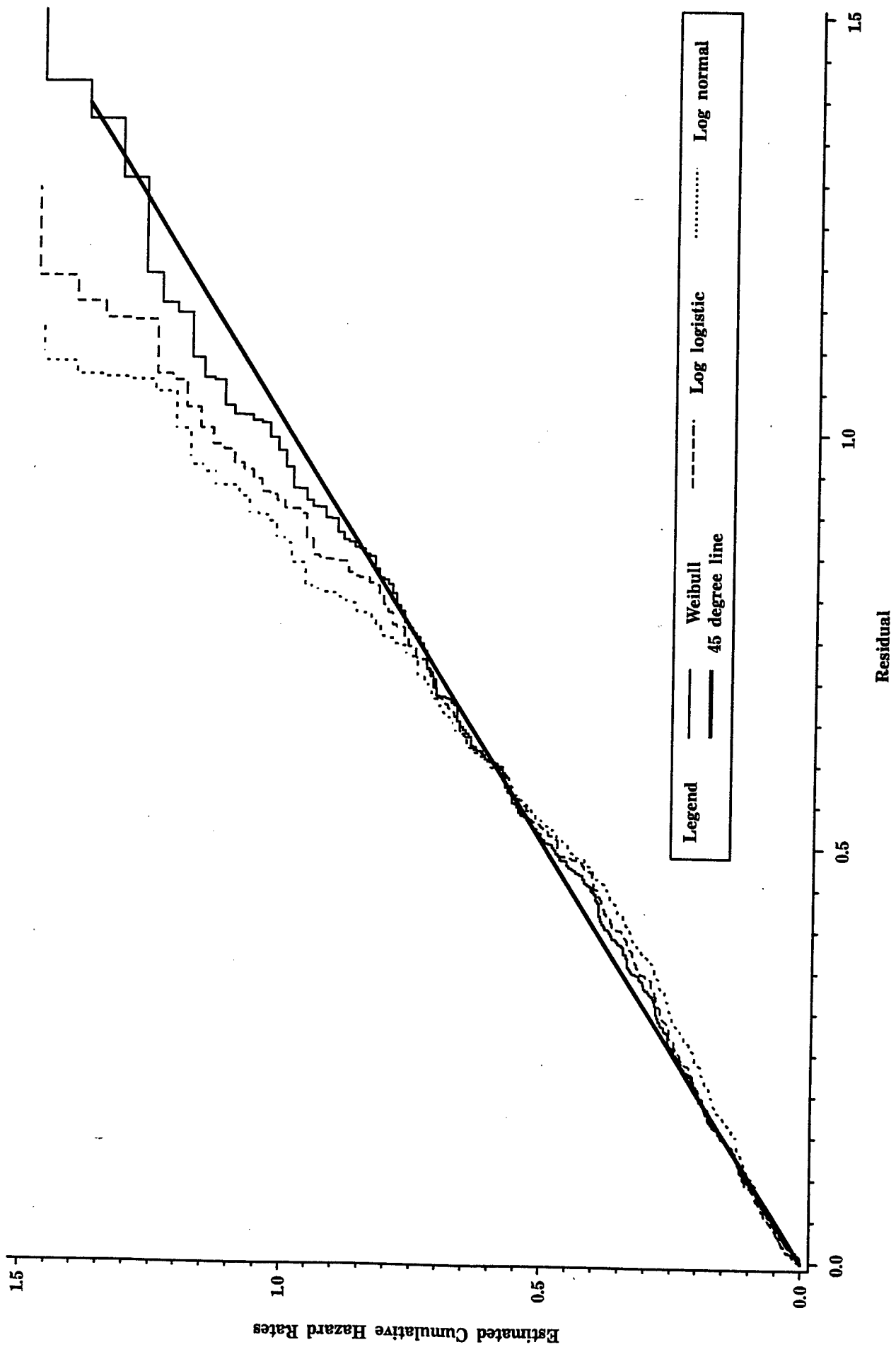
Figure 2

Plot of Difference of Ln(Ho(t)) for Condom Use

Legend   ——— Sometimes – Always   ··········   Never – Always

Days to Reinfection

Difference of Ln(Ho(t))
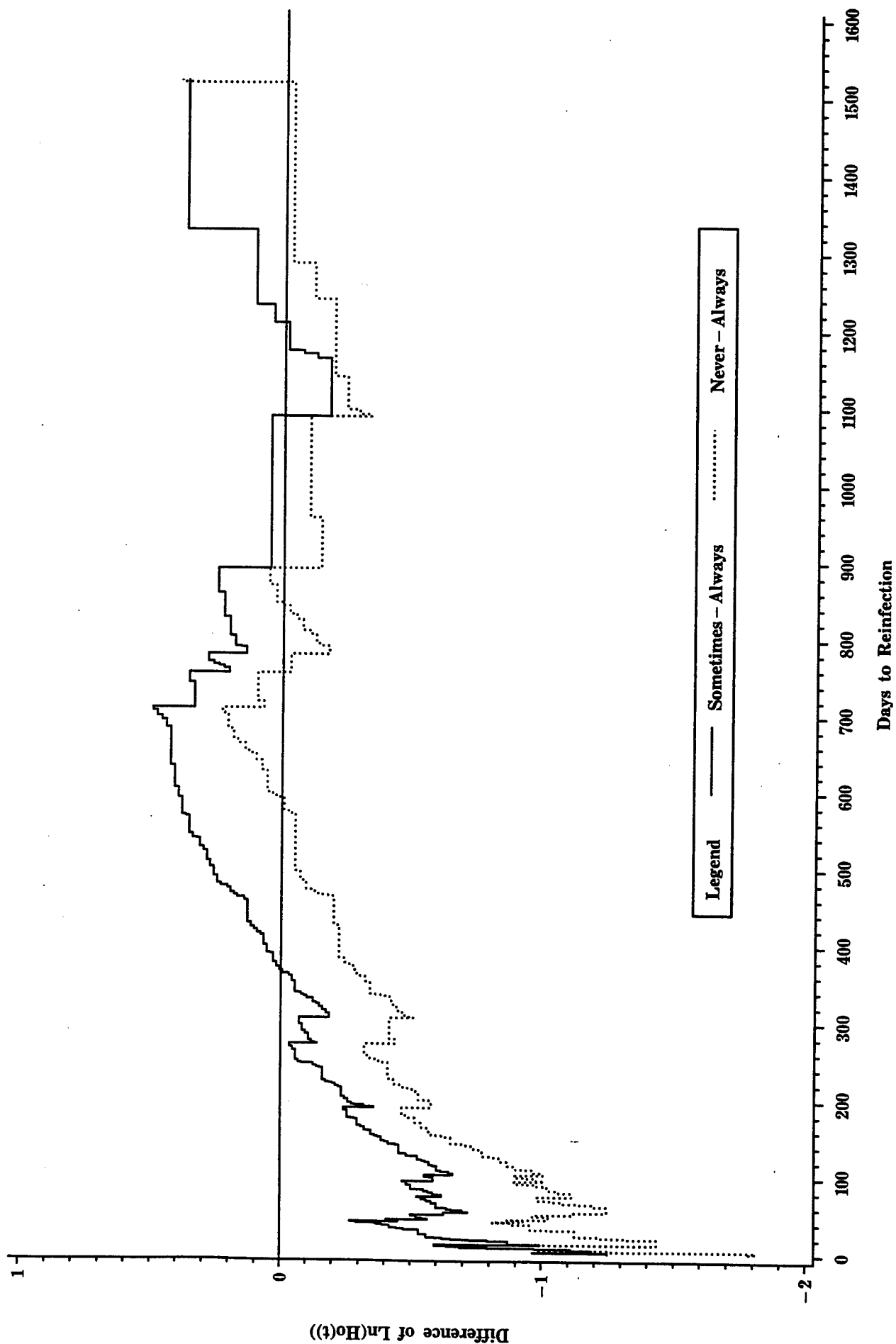
Figure 3
Plot of Ho(t) for Condom Use

Legend
——— Ho(t) for Sometimes Use Condom
········· Ho(t) for Never Use Condom

Ho(t) for Always Use Condom

Ho(t)
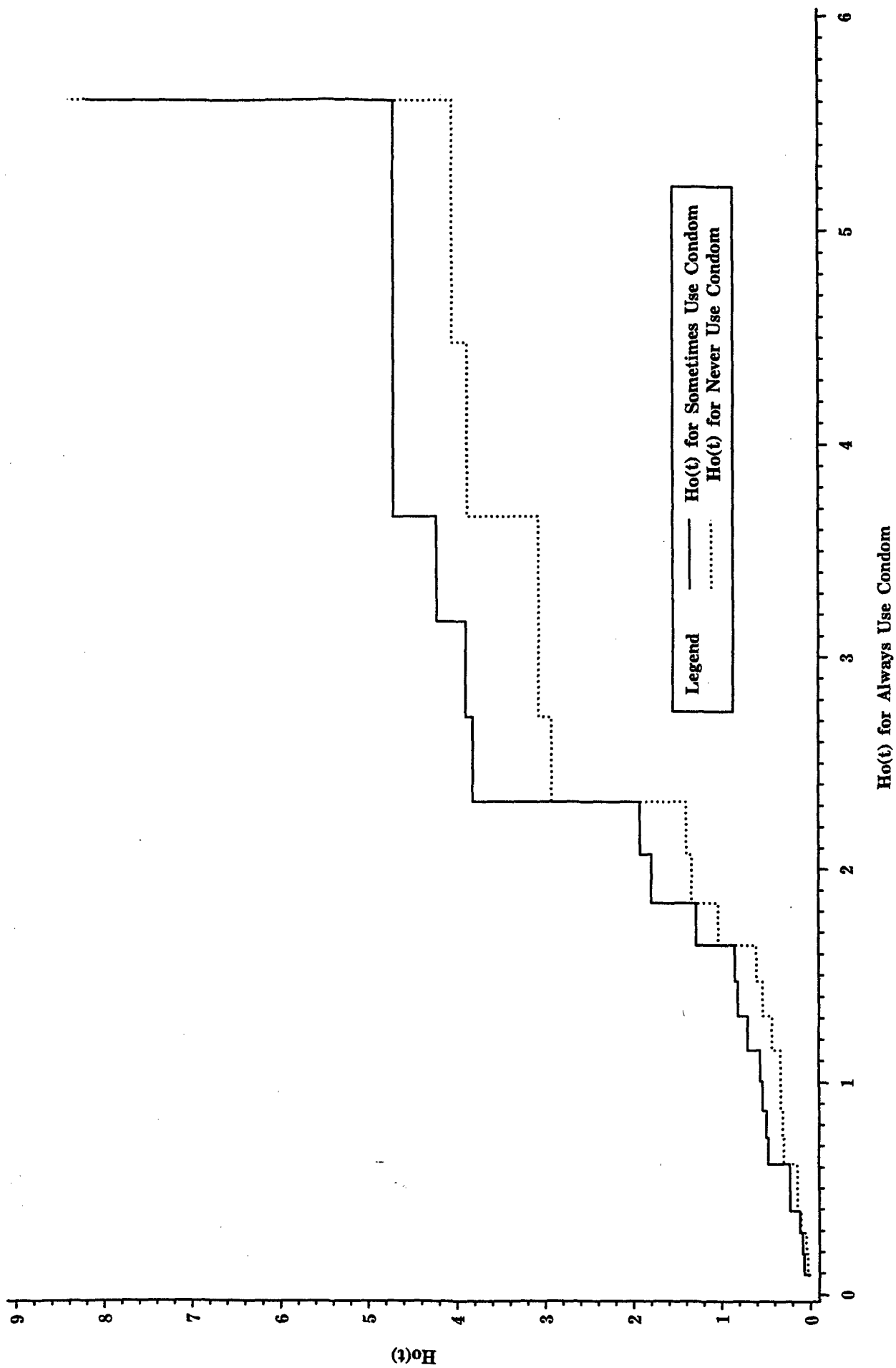
Figure 4
Martingale Residual Plot for Years of Schooling
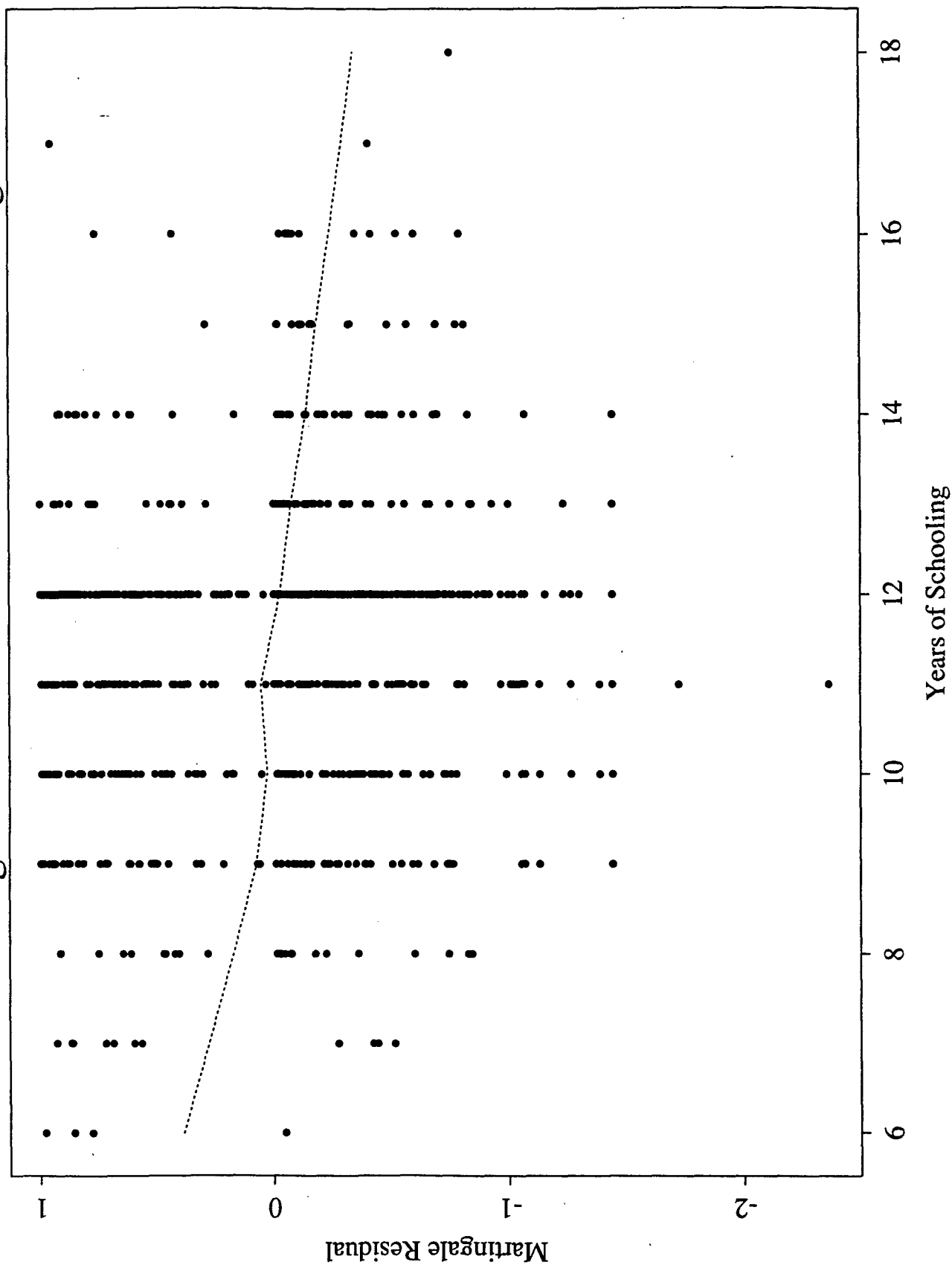
Figure 5

Deviance Residuals for Years of Schooling
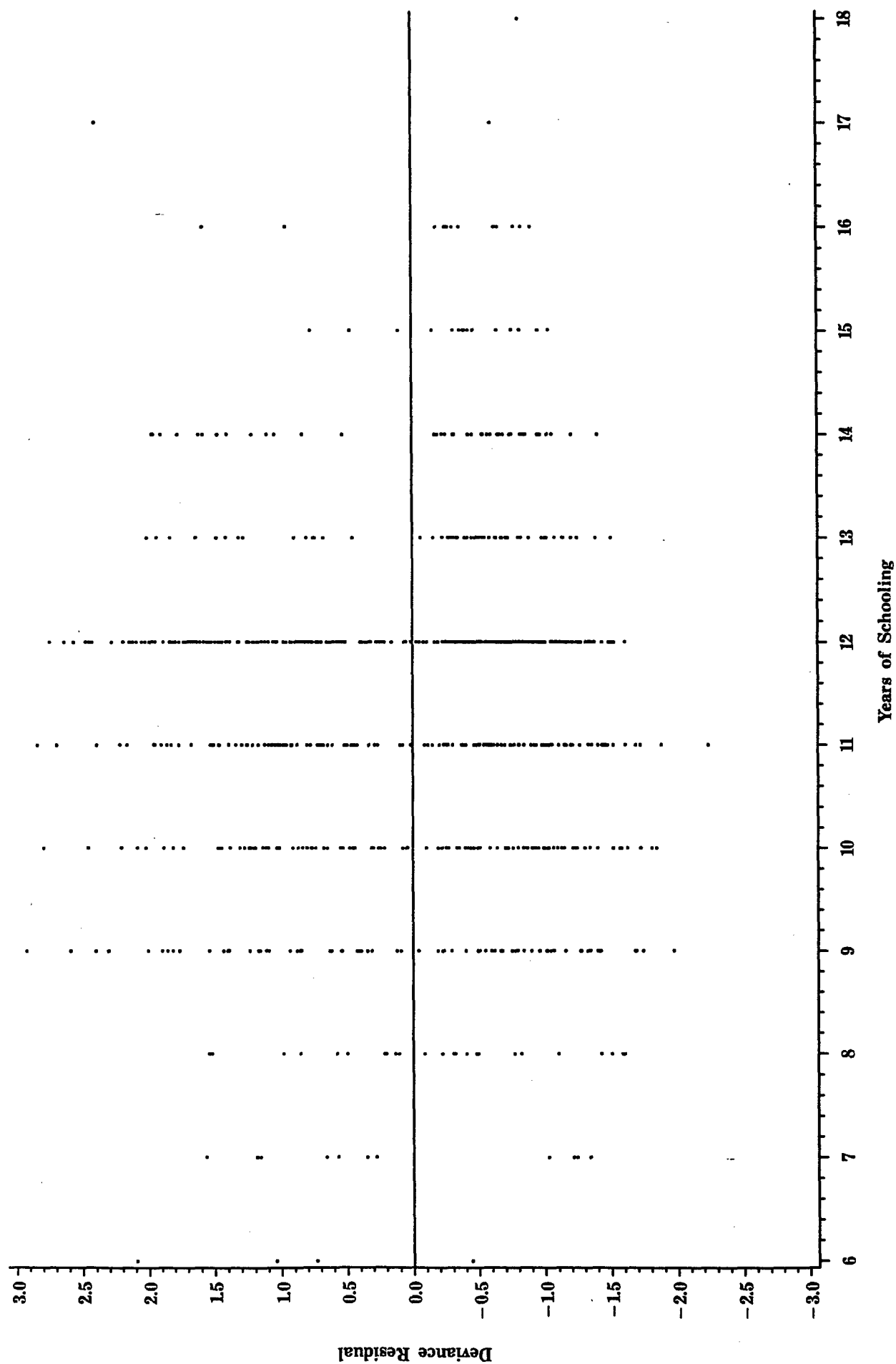
Figure 6

Standardized Score Residuals for Years of Schooling
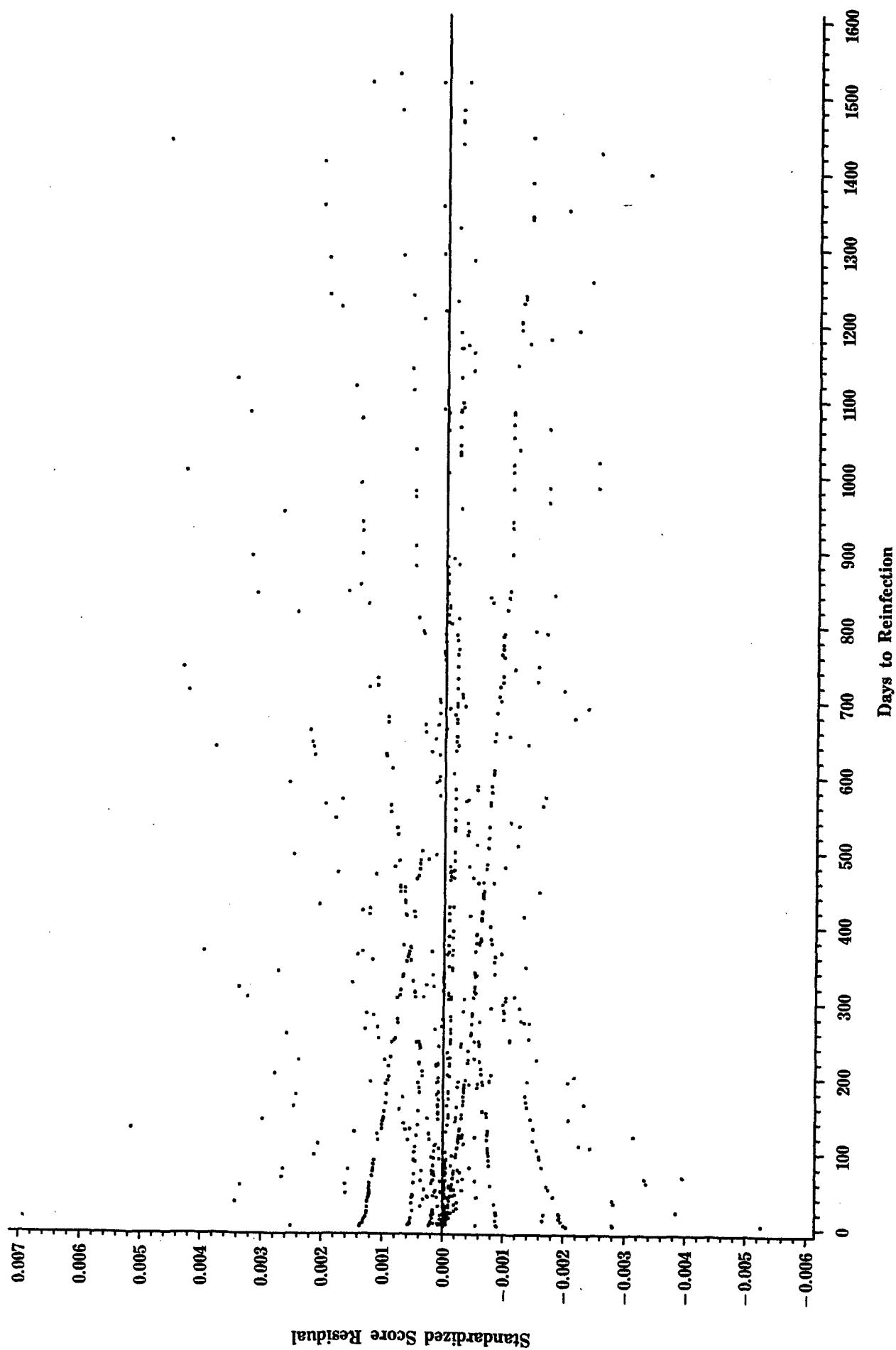
Figure 7

Standardized Score Residuals for Oral Sex in Last Year
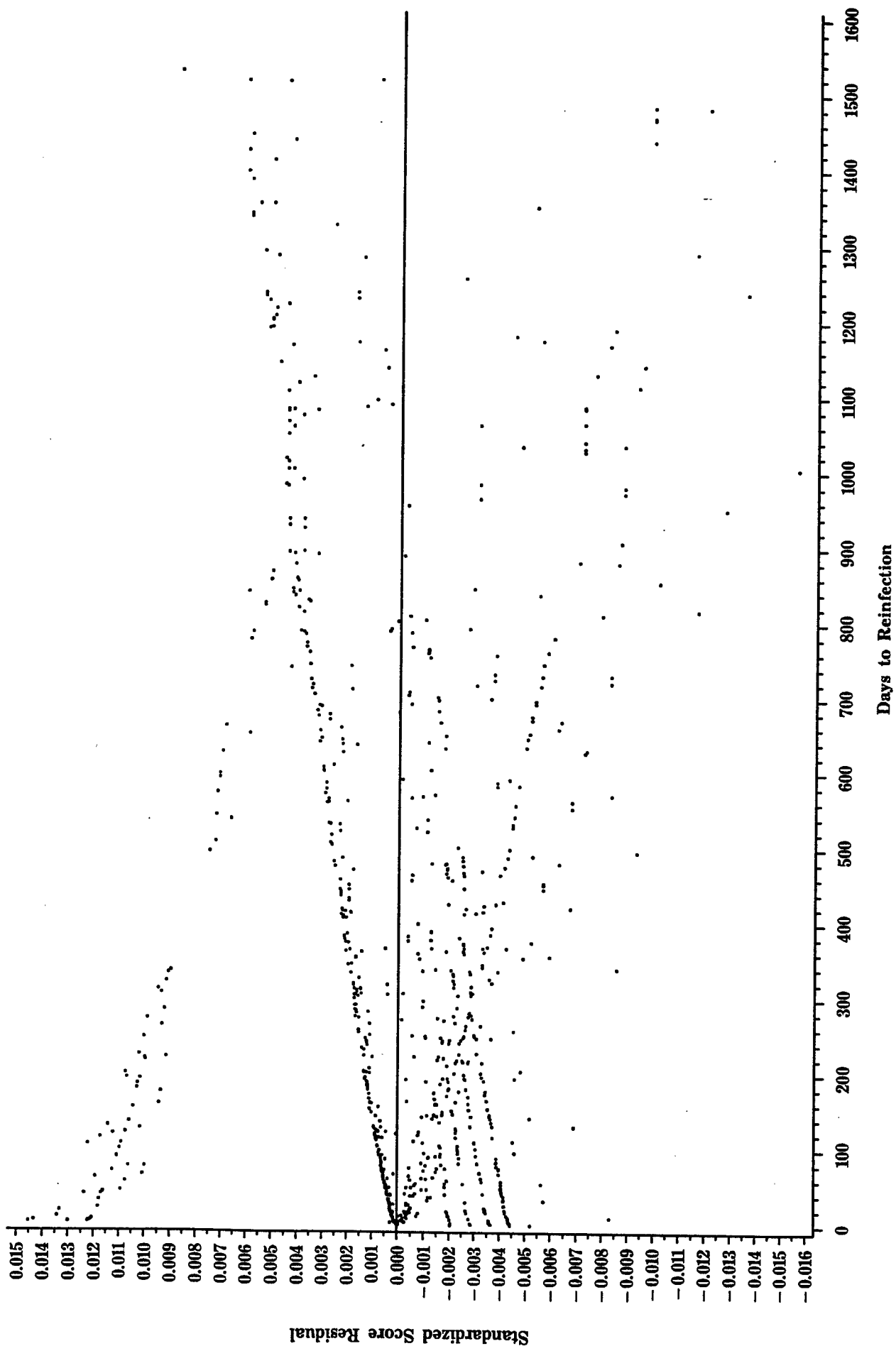
Figure 8
Estimate of Cumulative Baseline Hazard
and 95% Confidence Interval
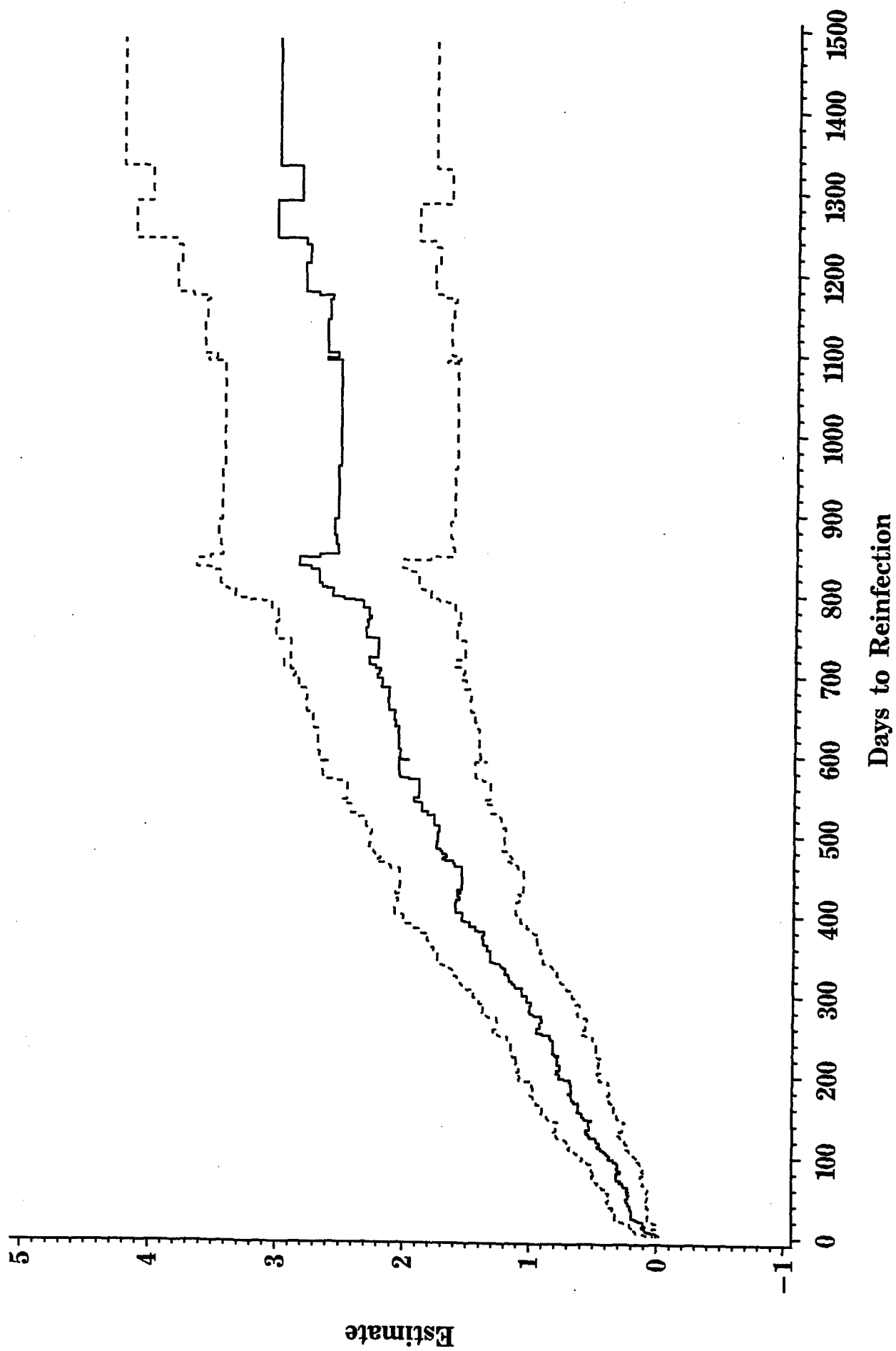
Figure 9

Estimate of Cumulative Excess Risk of Years of Schooling and 95% Confidence Interval
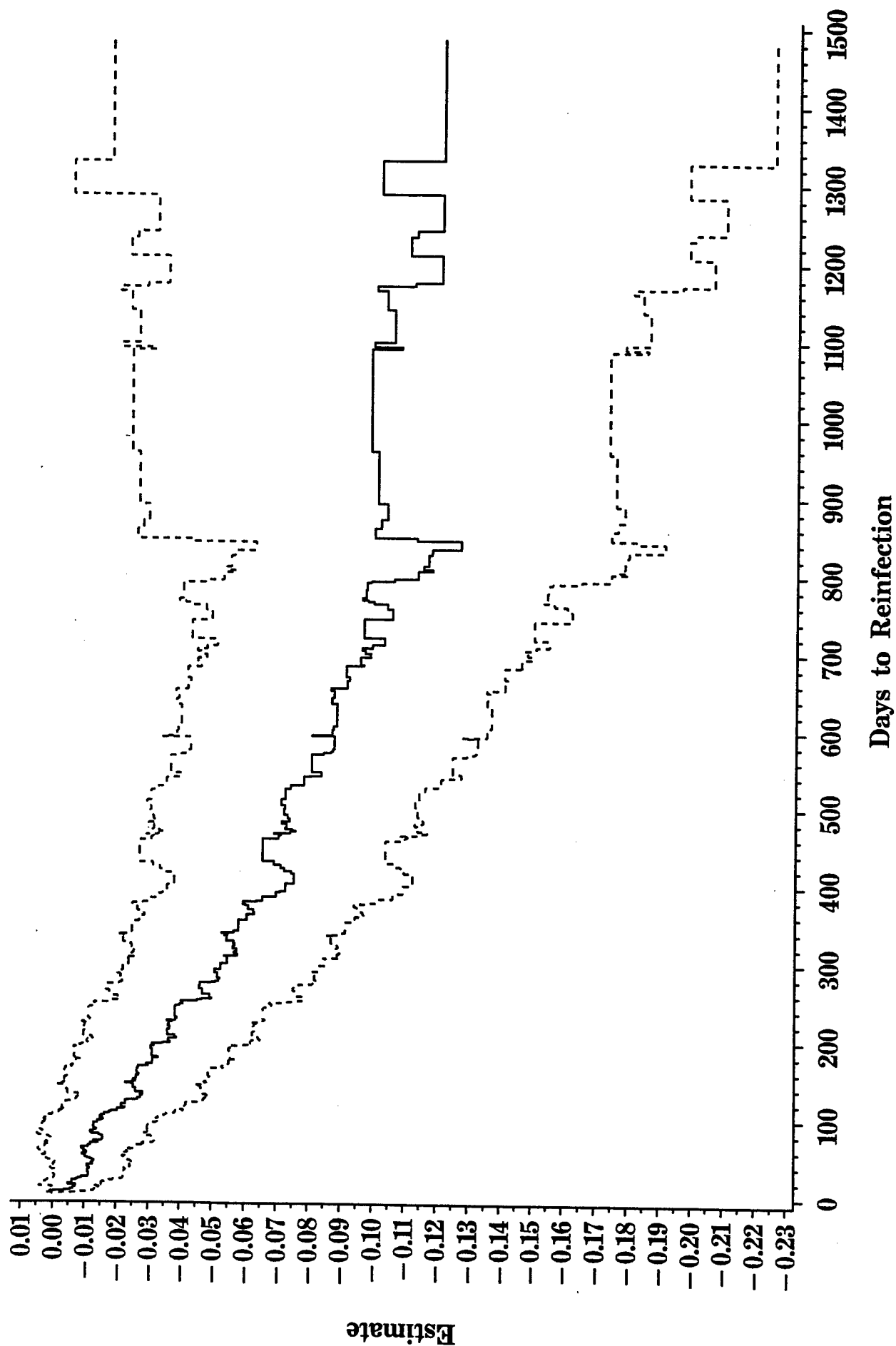
Figure 10

Estimate of Cumulative Excess Risk of Oral Sex in Last Year
and 95% Confidence Interval
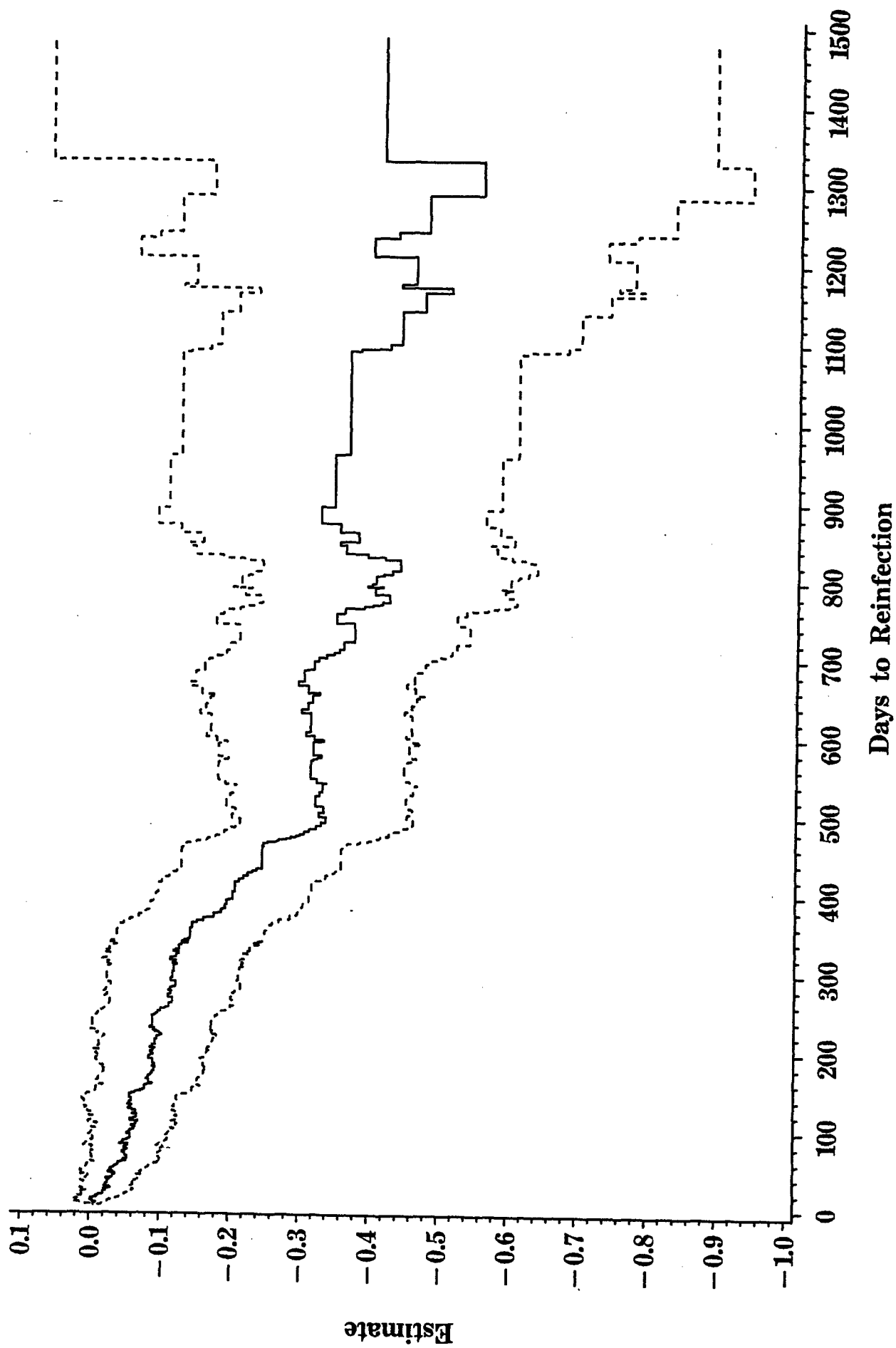
Figure 11

Estimate of Cumulative Excess Risk of Sometimes Using Condom Compared to Always and 95% Confidence Interval

Days to Reinfection
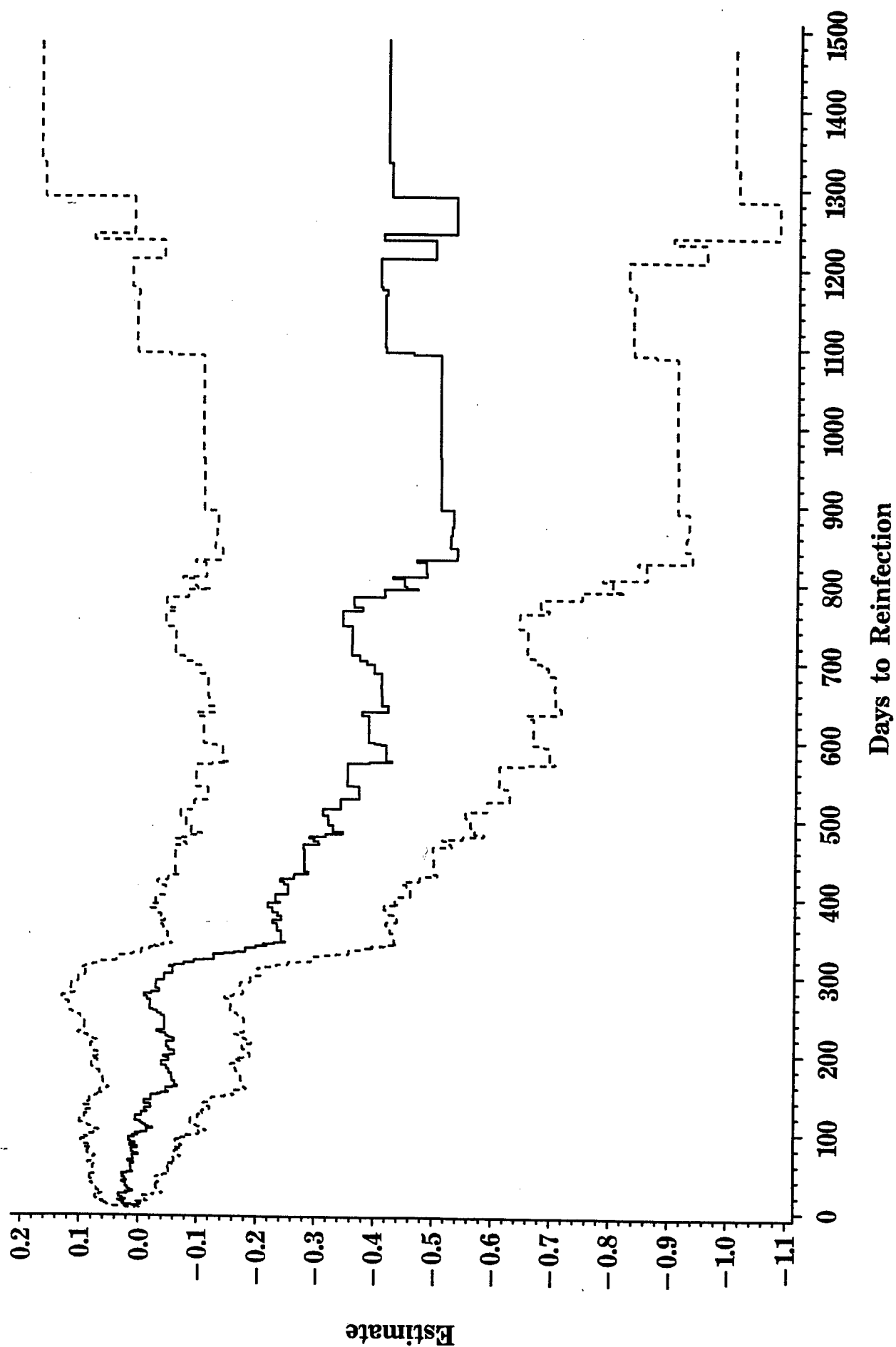
Estimate

Figure 12
Estimate of Cumulative Excess Risk of Never Using Condom
Compared to Always and 95% Confidence Interval
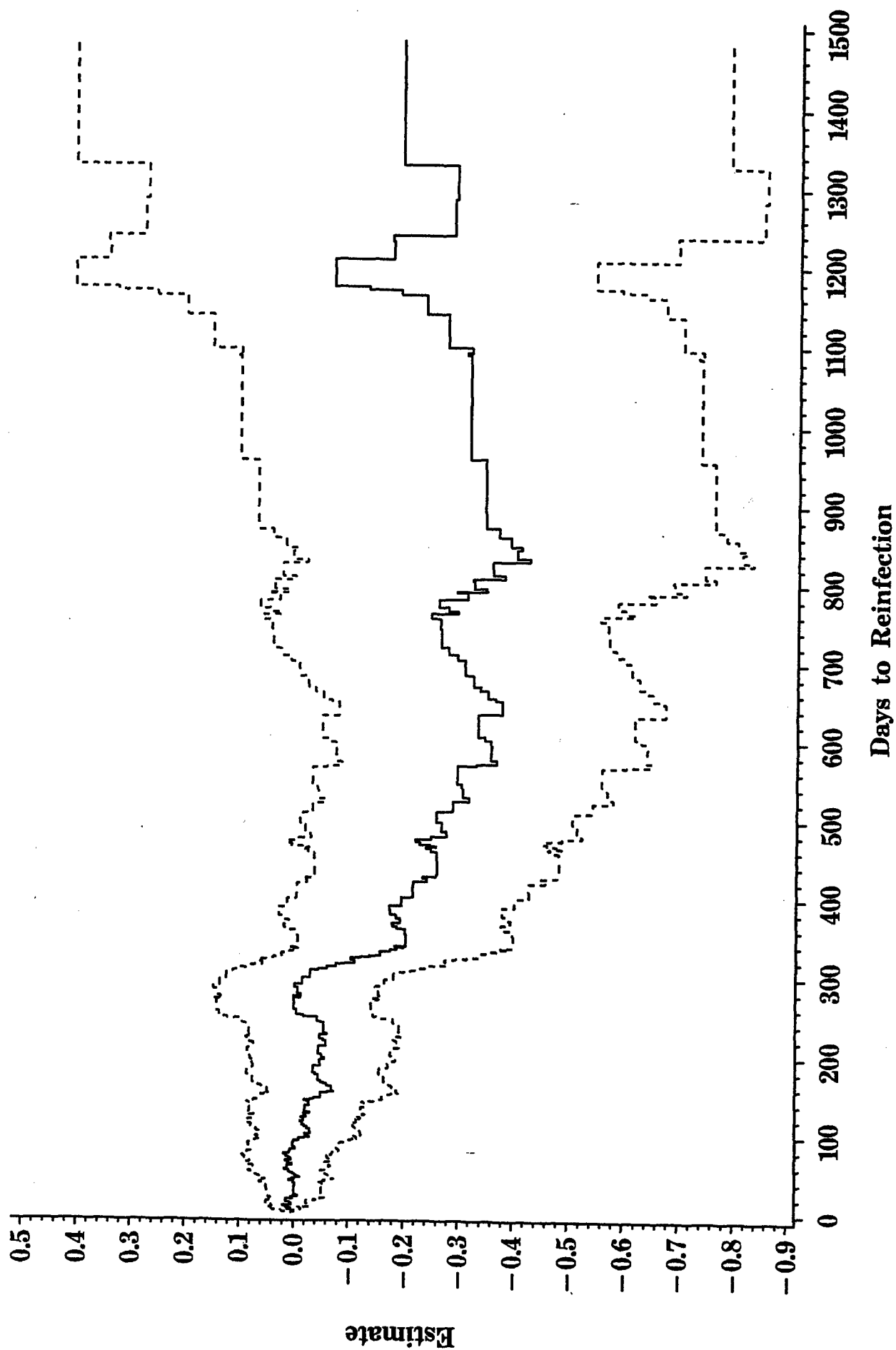
High-Dose Chemotherapy With Autologous Hematopoietic Stem-Cell Support for Breast Cancer in North America

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Purpose: To identify trends in high-dose therapy with autologous hematopoietic stem-cell support (autotransplants) for breast cancer (1989 to 1995).

Patients and Methods: Analysis of patients who received autotransplants and were reported to the Autologous Blood and Marrow Transplant Registry. Between January 1, 1989 and June 30, 1995, 19,291 autotransplants were reviewed; 5,886 were for breast cancer. Main outcomes were progression-free survival (PFS) and survival.

Results: Between 1989 and 1995, autotransplants for breast cancer increased sixfold. After 1992, breast cancer was the most common indication for autotransplant. Significant trends included increasing use for locally advanced rather than metastatic disease ($P < .00001$) and use of blood-derived rather than marrow-derived stem cells ($P < .00001$). One–hundred-day mortality decreased from 22% to 5% ($P < .0001$). Three-year

PFS probabilities were 65% (95% confidence intervals [CIs], 59 to 71) for stage 2 disease, and 60% (95% CI, 53 to 67) for stage 3 disease. In metastatic breast cancer, 3-year probabilities of PFS were 7% (95% CI, 4 to 10) for women with no response to conventional dose chemotherapy; 13% (95% CI, 9 to 17) for those with partial response; and 32% (95% CI, 27 to 37) for those with complete response. Eleven percent of women with stage 2/3 disease and less than 1% of those with stage 4 disease participated in national cooperative group randomized trials.

Conclusion: Autotransplants increasingly are used to treat breast cancer. One–hundred-day mortality has decreased substantially. Three-year survival is better in women with earlier stage disease and in those who respond to pretransplant chemotherapy.

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BREAST CANCER is the most common cancer and the second most common cause of cancer deaths in American women.[1] Survival of women with breast cancer correlates with extent of disease. Ten-year survival is 65% to 80% for women with disease confined to the breast.[2-4] Ten-year survival is 35% to 65% for those with one to three involved axillary lymph nodes, 30% to 40% for those with four to nine involved axillary nodes, and 15% to 30% in those with more than nine involved axillary nodes.[5-7] Recurrent disease tends to develop earlier in patients with multiple involved nodes and relapse risk persists for at least 20 years after mastectomy. Women with metastatic breast cancer have a median survival rate of approximately 2 years and a 2% to 5% probability of 5-year disease-free survival.[8-11]

Intensive therapy (high-dose chemotherapy with or without radiation therapy) with autologous hematopoietic stem-cell support (autotransplant) is increasingly used to treat breast cancer in women at high risk of persistent or recurrent disease. However, most reports of autotransplants include relatively few subjects and there are likely to be substantial reporting biases. One small randomized study of women with metastatic breast cancer shows a statistically significant advantage in both survival and disease-free survival for high-dose chemotherapy with bone marrow transplant versus conventional-dose chemotherapy.[12] Here we report results of autotransplants in more than 5,800 consecutive women receiving autotransplants at over 130 centers between 1989 and 1995.

METHODS

Patients

The Autologous Blood and Marrow Transplant Registry of North America (ABMTR) is a voluntary organization of more than 170 transplant institutions in the United States, Canada, and Central and South America that report data on consecutive autotransplants to a Statistical Center at the Medical College of Wisconsin. An autotransplant is defined as treatment with a sufficiently high dose of chemotherapy to require autologous bone marrow or blood-derived hematopoietic stem-cell support. The Statistical Center also collects data for allogeneic blood and bone marrow transplants (allotransplants) from centers that participate in the International Bone Marrow Transplant Registry, a similar but independent organization of allotransplant centers worldwide.

The ABMTR began data collection in 1992. Data were collected retrospectively for patients who received autotransplants between 1989 and 1992 and prospectively thereafter. Participating centers register basic information on consecutive autotransplants for all disease indications. Based on data collected in the Centers for Disease Control Hospital Surveys,[13,14] approximately half of North American autotransplants for all diseases were registered with the ABMTR during the study period. A list of participating centers is shown in the Appendix. Registration data from consecutive women with breast cancer who received an autotransplant at ABMTR centers between January 1, 1989 and June 30, 1995 were the subject of this analysis.

Data regarding disease type, age, sex, and posttransplant survival

were requested for all patients. Questions regarding pretransplant disease stage and chemotherapy responsiveness, date of diagnosis, graft type (bone marrow and/or blood-derived stem cells), high-dose conditioning regimen, and posttransplant disease progression were added to registration forms more recently. Although an attempt was made to collect this information for previously registered patients, these data are not available for all patients. Patients with primary (stages 2, 3, and inflammatory) and metastatic breast cancer were considered separately in the analysis. The ABMTR requests data on progression or death in registered patients at 6-month intervals.

Statistical Methods

Comparisons of patient and treatment characteristics over time used χ^2 test for categorical and Kruskal-Wallis test for continuous variables.[15] Probabilities of 100-day mortality (death in the first 100 days as a result of toxicity, disease progression, or both), progression-free survival (PFS), and overall survival were calculated using the Kaplan-Meier product limit estimate.[16] The log-rank test was used for comparisons of 100-day mortality, PFS, and survival between groups.[17]

RESULTS

Between January 1, 1989 and June 30, 1995, 19,291 patients receiving high-dose therapy with autologous hematopoietic stem-cell support were registered with the ABMTR. Of these, 5,886 (31%) had breast cancer. Between 1989 and 1995, autotransplants for breast cancer increased from 16% to 40% ($P < .00001$) of all autotransplants registered (Fig 1, Table 1). Numbers of autotransplants for breast cancer exceeded those for Hodgkin disease and non-Hodgkin lymphoma after 1992. By 1993 to 1994, breast cancer was the most common indication for stem-cell transplants of all types (Fig 1).

Numbers of patients reported per year, age at transplant, pretransplant disease stage, source of stem cells, and 100-day mortality are listed in Table 1. The distribution of disease stage at transplantation changed from 7% local and 93% metastatic disease in 1989 to approxi-
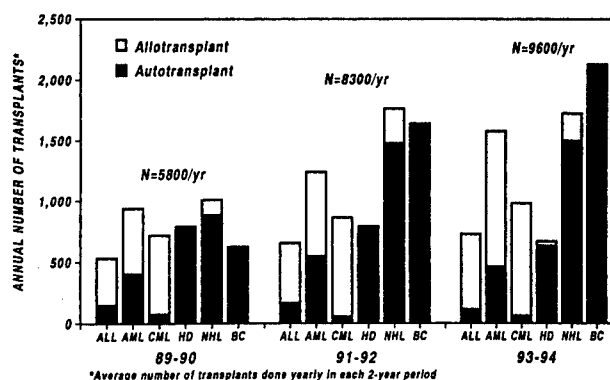
Fig 1. Numbers of allotransplants (hematopoietic stem cells collected from a donor) and autotransplants by year by disease for most common indications.

Table 1. Autotransplants for Breast Cancer Registered With the ABMTR

	1989	1990	1991	1992	1993	1994	January to June 1995	P
No. of patients	272	342	683	1,069	1,189	1,513	818	
Percent of all autotransplants registered	16	16	25	33	33	39	40	< .00001
Autotransplants for breast cancer								
No. of centers reporting	34	45	66	85	99	105	101	
Median transplants per center	3	5	6	7	6	8	5	.005
Range	1-58	1-44	1-44	1-71	1-59	1-86	1-63	
Stage immediately before high-dose chemotherapy and autotransplant								
No. assessable*	213	313	650	1,005	1,088	1,404	721	< .00001
Local diseaset (%)	7	16	23	34	31	39	49	
Metastatic (%)	93	83	77	65	68	60	50	
Other‡ (%)	< 1	1	< 1	1	1	1	1	
Age, years								
No. assessable	272	341	678	1,059	1,123	1,461	817	< .00001
Median	41	42	44	44	45	45	45	
Range	23-64	24-66	22-72	25-65	24-66	22-69	22-71	
Interval diagnosis to transplant (years)								
No. assessable	237	299	614	960	1,106	1,392	774	< .00001
< 1 (%)	18	24	31	44	42	49	57	
1-2 (%)	28	19	16	14	12	13	10	
> 2 (%)	54	57	53	42	46	38	33	
Graft type								
No. assessable	162	215	474	813	1,189	1,447	760	< .00001
BM (%)	81	79	58	42	30	19	10	
BM + PBSC (%)	5	7	22	33	30	25	18	
PBSC (%)	14	14	20	25	40	56	72	
Conditioning regimen								
No. assessable	140	183	423	735	870	1,174	587	< .00001
CBP (%)	7	4	11	13	9	14	6	
CT (%)	25	22	23	23	21	21	21	
CTCb (%)	18	16	15	28	37	39	44	
CTM (%)	6	2	6	4	4	2	1	
ICE (%)	3	10	8	7	6	4	4	
CTHu (%)	8	4	5	4	3	3	4	
CEP (%)	3	3	5	3	2	1	2	
Other (%)	30	37	27	18	18	16	18	
100-day mortality								
No. assessable	265	340	679	1,034	1,153	1,366	784	< .00001
%	22	15	11	6	6	4	5	

Abbreviations: BM, bone marrow; PBSC, peripheral-blood stem cells; C, cyclophosphamide; B, carmustine; P, cisplatin, T, thiotepa, Cb, carboplatin; M, mitoxantrone; I, ifosfamide; E, etoposide; Hu, hydroxyurea.

*Information for all variables not available for all patients; registration forms were revised in 1992 and 1993 to capture additional information.

tLocal disease = stage 2, 3; and inflammatory breast cancer.

‡Patients with locally persistent or recurrent disease post–conventional therapy.

mately 50% local and 50% metastatic disease in 1995 (P < .00001). This is reflected in the interval from diagnosis to transplant, which decreased over the study period. By 1995, 57% of transplants for breast cancer were performed within 1 year of diagnosis.

Use of blood-derived cells alone or in combination with bone marrow increased from 19% to 90% (P < .00001) in these 6 years. Various preparatory regimens were used, with only the combination of cyclophosphamide, thiotepa, and carboplatin (CTCb) used in more than 25% of all

patients. An important finding was decreasing 100-day mortality, from 22% in 1989 to 5% in 1995 (P < .00001).

High-Risk Primary Breast Cancer

Characteristics of women who received autotransplants for stage 2, 3, and inflammatory breast cancer are listed in Table 2. Eleven percent were treated as part of randomized cooperative group trials. Although most patients had stage 2 or 3 breast cancer and ≥ 10 involved axillary nodes, some transplants were performed for inflammatory

Table 2. Autotransplants for Stage 2, 3, or Inflammatory Breast Cancer

	No. assessable*	No.	%
No. registered	1,747		—
Median age, years	1,731	44	
Range		22-69	
Stage pretransplant			
2	1,613†	750	46
3		603	37
Inflammatory		260	17
Months from diagnosis to transplant	1,636	7	
Range		2-16	
No. of nodes positive	542		
< 10		150	28
≥ 10		392	72
ER positive	479	298	62
Principal adjuvant chemotherapy			
CAF	491	314	64
Graft type	1,527		
BM		502	32
BM + PBSC		450	30
PBSC		555	38
High-dose chemotherapy regimen used	1,370		
CT		432	32
CTCb		403	29
CBP		220	16
CTM		52	4
ICE		78	6
CEP		26	2
Other		156	11
100-day mortality (%)	1,668		3

Abbreviations: ER, estrogen receptor; C, cyclophosphamide; A, doxorubicin; F, fluorouracil; BM, bone marrow; PBSC, peripheral-blood stem cells; B, carmustine; P, cisplatin; T, thiotepa; Cb, carboplatin; M, mitoxantrone; E, etoposide; Hu, hydroxyurea.

*Information for all variables not available for all patients. Registration forms were revised in 1992 and 1993 to capture additional information.

†One hundred thirty-four additional patients stage 2 v 3 v inflammatory not specified.

breast cancer (17%) or for women with less than 10 involved axillary nodes (28%). Kaplan-Meier estimates of survival and PFS by disease stage are shown in Fig 2; 3-year probabilities are listed in Table 3.

Metastatic Breast Cancer

Characteristics of women who received autotransplants for metastatic breast cancer are listed in Table 4. Fewer than 1% were treated on randomized cooperative group trials. Most patients had chemotherapy-sensitive disease (complete or partial response before transplant) and either visceral or bone disease. Median survival was 19 months (Fig 2). Three-year PFS and survival probabilities are listed in Table 3. Women with a complete response to chemotherapy pretransplant had higher survival and PFS than those with either a partial response or resistant disease (Fig 3).

Second Malignancies

Data regarding second malignancies were available for 2,045 women. There were 13 cancers reported: four myelodysplastic syndromes, two endometrial carcinomas, one ovarian carcinoma, one squamous cell carcinoma, one transitional cell carcinoma of the bladder, one Hurthle cell tumor of the thyroid, one lung carcinoma, one glioblastoma, and one cervical cancer.

DISCUSSION

These data indicate several interesting aspects of autotransplants for breast cancer. First, the annual frequency of autotransplants has increased substantially, from fewer than 300 reported to the ABMTR in 1989 to approximately 1,500 presently. Second, an increasing proportion are for women with locally advanced disease: less than 10% in 1989 versus approximately 50% presently. As a correlate, the interval from diagnosis to transplant has decreased substantially; less than 20% of transplants were performed within 1 year of diagnosis in 1989 versus more than 50% presently. A third trend is increasing use of blood-derived rather than bone marrow−derived grafts: 14% in 1989 versus more than 70% presently. Finally, 100-day mortality also decreased substantially, from more than 20% in 1989 versus 5% presently. This probably reflects several factors, including selection of patients with less advanced disease and better performance status.

Women with locally advanced (stage 2 and 3) breast cancer who receive autotransplants differ from the general population of women presenting with breast cancer. Median age was 44 years and more than 70% had more than nine involved lymph nodes. These data contrast with typical women with breast cancer, whose median age is approximately 60 years, of whom approximately 5% have more than nine involved lymph nodes.[6,7] These differences reflect the substantial selection factors for transplant and underscore the importance of comparing autotransplants and chemotherapy in comparable subjects. A Toronto study reported that 28% of patients referred for one randomized trial of high- versus lower-dose therapy were ineligible because of occult metastatic disease identified by the required pretransplant evaluation.[18] Thus, differences observed between patients who received autotransplants and those who received conventional-dose chemotherapy in historical data bases may result from selection of patients without occult metastases.

Women with metastatic (stage 4) disease who received autotransplants were also somewhat atypical. Median age was 44 years and 58% had cancers with estrogen receptors. Approximately 28% had a complete response to chemotherapy, but 24% had disease progression. These data contrast with typical women with stage 4 breast cancer

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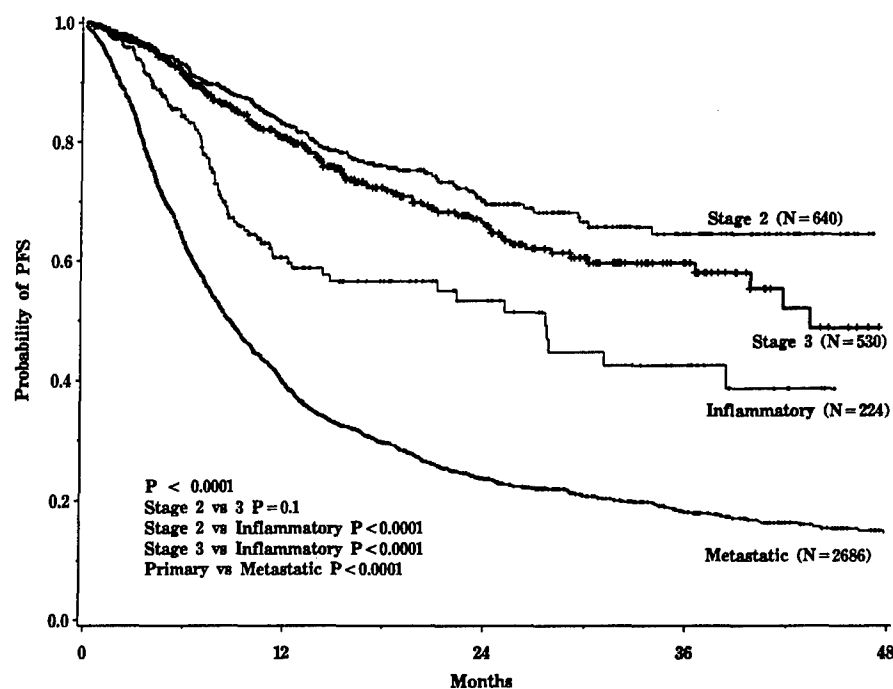
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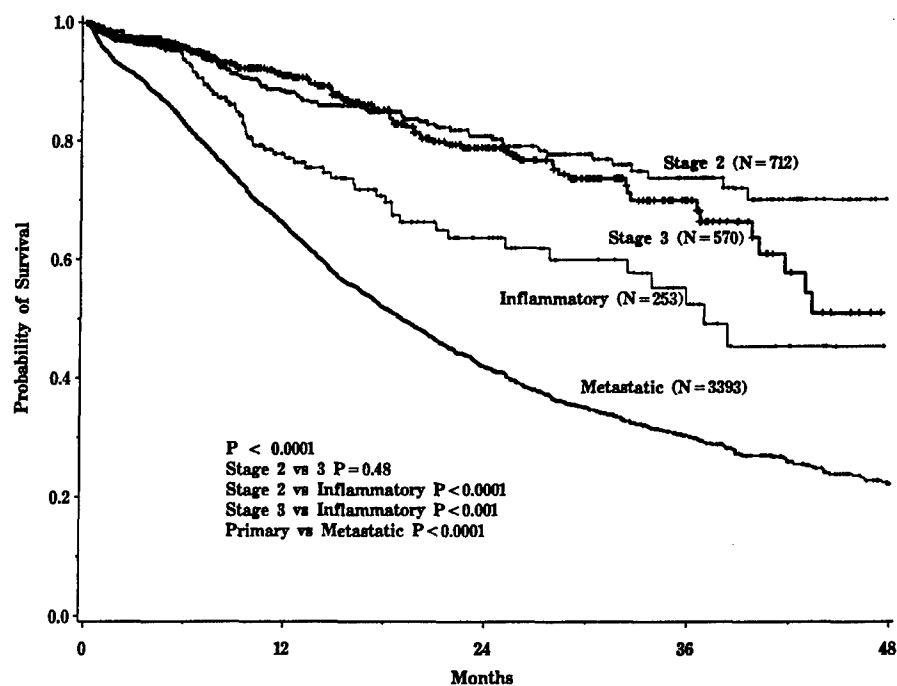
Fig 2. Kaplan-Meier estimates of PFS (A) and survival (B) after auto-transplants for primary (stage 2, 3, or inflammatory) and metastatic breast cancer.

Table 3. Three-year Kaplan-Meier Estimates of PFS and Overall Survival After Autotransplants for Breast Cancer

Stage	PFS (%)	95% CI	Survival (%)	95% CI
2 (2 to 5 cm or involved lymph nodes)	65	59-71	74	68-80
3 (> 5 cm or fixed to the chest wall)	60	53-67	70	63-77
Inflammatory	42	31-53	52	40-64
Metastatic	18	16-20	30	28-32
Response to chemotherapy				
In complete remission	32	27-37	46	40-52
In partial remission	13	9-17	29	25-33
Not responding	7	4-10	16	12-20

whose median age is approximately 60 years, of whom 60% to 70% have cancers with estrogen receptors. These differences again underscore the importance of comparing autotransplants and chemotherapy in comparable subjects. Nevertheless, one small randomized study showed a statistically significant advantage in both survival and disease-free survival for high-dose chemotherapy with bone marrow transplant versus conventional-dose chemotherapy in women with metastatic disease.[12]

Results of autotransplants correlated with disease stage. Women with stage 2 or 3 disease had better PFS and survival than those with stage 4 disease. However, there was no difference in PFS or survival between women with stage 2 versus 3 disease. Among women with metastatic (stage 4) disease, those with a complete response to pretransplant chemotherapy fared better than those with a partial response. The latter fared better than those with stable disease or progression. Women with tumors unresponsive to lower-dose treatment are very unlikely to achieve long-term disease-free survival after autotransplant.

The correlation between stage and chemotherapy response and outcome is not surprising. Similar results are reported for conventional treatments. Better transplant outcome in "better" subjects does not mean that transplants should be performed earlier or indicate whether transplants are better than conventional therapy. These questions are best addressed in prospective studies, several of which are underway (Table 5). In this survey, only 11% of women with stage 2 or 3 disease and fewer than 1% of those with stage 4 disease participated in national cooperative group randomized trials. During the time covered by this survey, three cooperative group trials were open for enrollment in the United States, one for metastatic disease and two for adjuvant therapy. Additionally, randomized trials, including the one published study[12] and those listed in Table 5, are not designed to answer other important questions such as relative efficacy of various high-dose regimens, supportive care technologies, or even patient-, disease-, and treatment-related factors important

for transplant outcome. The ABMTR is an important resource for addressing such issues. Data collected by the Centers for Disease Control hospital survey[13,14] suggest that approximately half of all autotransplants in North America are reported to the ABMTR. We believe that reporting of autotransplants for breast cancer is similar, making available a substantial proportion of cases for study. Registry audits ensure that this sample is unselected and that data are accurate. Because participation in the ABMTR is voluntary, it is possible that participating centers differ from nonparticipating centers. For example, nonacademic centers may be less likely to participate than academic centers, although the ABMTR includes many

Table 4. Autotransplants for Metastatic Breast Cancer

	No. assessable*	No.	%
No. registered	3,451		
Median age, years	3,398	44	
Range		22-72	
Sensitivity to chemotherapy pretransplant	3,411		
Complete or partial response		2,134	63
Stable or progressive disease		595	17
Undetermined		682	20
Sites of metastatic disease	1,212		
Viscera (no CNS)†		593	49
Bone or bone marrow ± soft tissue‡		328	27
Soft tissue alone		273	23
CNS§		18	1
ER positive	1,203	700	58
Interval, diagnosis to transplant (years)	3,298		
< 1		687	21
1-2		568	17
> 2		2,038	62
Graft type	3,018		
BM		993	33
PBSC		1,373	46
BM + PBSC		652	21
Conditioning regimen	2,522		
CTCb		899	36
CT		416	17
ICE		132	5
CTHu		146	6
CTM		71	3
CBP		202	8
CEP		60	2
Other		596	23
100-day mortality (%)	3,395		10

Abbreviations: ER, estrogen receptor; BM, bone marrow; PBSC, peripheral-blood stem cells; C, cyclophosphamide; B, carmustine; P, cisplatin, T, thiotepa; Cb, carboplatin; M, mitoxantrone; E, etoposide; Hu, hydroxyurea.

*Information for all variables not available for all patients. Registration forms were revised in 1992 and 1993 to capture additional information.

†Includes patients with or without bone, bone marrow, or soft tissue involvement.

‡Excludes patients with visceral or CNS involvement.

§Includes patients with or without visceral, bone, bone marrow, or soft tissue involvement.

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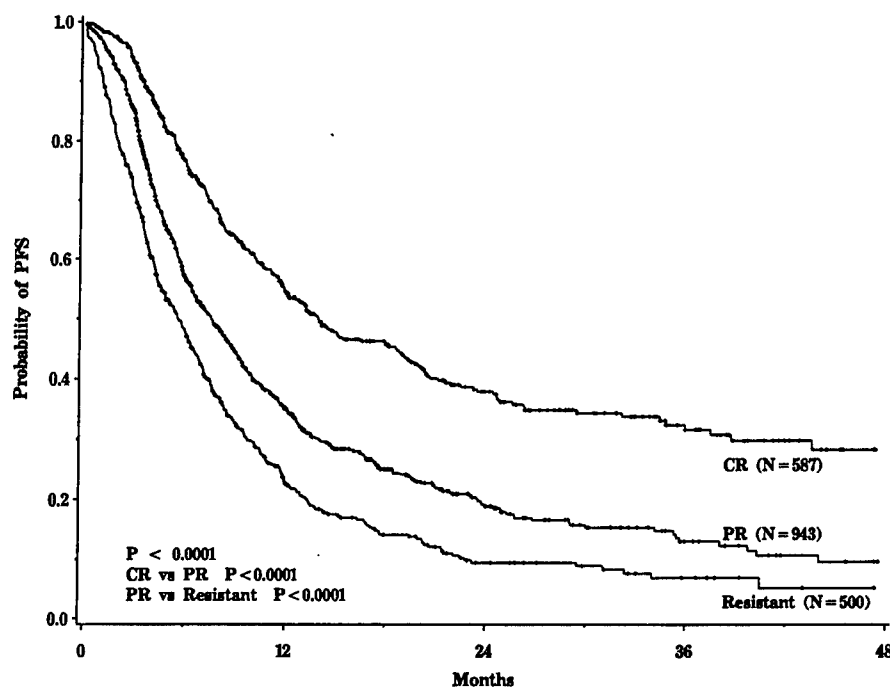
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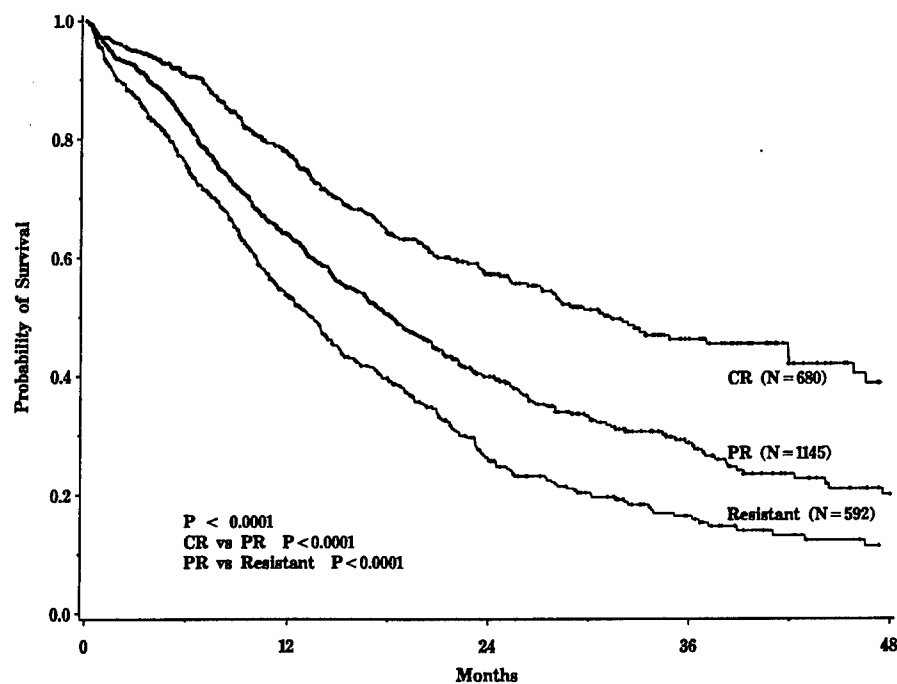
Fig 3. Kaplan-Meier estimates of PFS (A) and survival (B) after autotransplant for metastatic breast cancer by responsiveness to chemotherapy pretransplant. CR, complete response to conventional-dose chemotherapy pretransplant; PR, partial response; resistant, stable or progressive disease pretransplant.

Table 5. Ongoing Randomized Trials of Autotransplants in Breast Cancer by Stage

Eligible Stage	Study Sponsor	Standard Initial Therapy	High-dose Regimen	Control
Stage 2				
No. of involved lymph nodes				
≥ 4	Milan/Italy	None	HDS	E × 3, CMF × 6
≥ 4	Inter-Scandinavian	CEF × 4	CTCb	CEF × 4
≥ 4	Italian	CEF × 4	CEL	CEF × 2
≥ 4	Dutch	CEF × 4	CTCb	CEF × 1
4-9	Duke	AF	CBP	No more therapy v CBP alone
≥ 6	ICG (Manchester)	CE × 4	CTCb	CE × 4
≥ 8	SFGM/FNCCC	CEF × 4	CMitoxL	No further therapy
≥ 10 or > 4 high risk	IBCSG		CE × 3	AC or EC × 4, then CMF × 3
≥ 10	CALGB	CAF × 4	CBP	Conventional-dose CBP
≥ 10	German Multicenter	CE × 4	CTMitox	CMF × 3
≥ 10	ECOG	CAF × 4	CT	No further therapy
Stage 3				
	Milan/Italy	None	HDS	E × 3, then CMF × 6
	SFGM/FNCCC	Chemotherapy × 4	CMitoxL	Conventional chemotherapy
	IBCSG		CE × 3	AC or EC × 4, then CMF × 3
	CALGB	A × 4	CTCb	Continuous CMF × 16 weeks
	German Multicenter	CE × 4	CTMitox	CMF × 3
Stage 4				
	Duke (CRs only)	AFM × 4	CBP	CBP at relapse
	Duke (bone only)	AFM × 4, radiation	CBP	CBP at relapse
	Philadelphia Intergroup	CAF × 6	CTCb	CMF × 2 years
	SFGM/FNCCC	Chemotherapy × 4	CMitoxL	Conventional chemotherapy

Abbreviations: ICG, International Collaborative Group (Manchester); SFGM, Societe Francaise de Greffe du Muelle; FNLCC, Federation Nationale des Centres de Lulte Centra le Cancer; CALGB, Cancer and Leukemia Group B; ECOG, Eastern Cooperative Oncology Group; SWOG, Southwest Oncology Group; IBCSG, International Breast Cancer Study Group; C, cyclophosphamide; E, epirubicin; A, doxorubicin; F, fluorouracil; Cb, carboplatin; M, methotrexate; P, cisplatin; L, melphalan; Mitox, mitoxantrone; T, thiotepa; HDS, high-dose sequential therapy.

nonacademic centers. It is also possible that centers with poorer results do not report their data, although outcomes in our analyses are similar to those of large nonparticipating centers. Of interest, prior surveys of worldwide allogeneic transplant activity[19-21] suggest that centers in the IBMTR are similar to nonparticipating centers in characteristics and outcome. Finally, analyses of differences among centers are difficult for centers that perform fewer than 30 autotransplants. However, small centers, considered as a group, did not perform worse than large centers

in this study. The ABMTR provides an important observational data base that will complement data from randomized trials and with which one can monitor trends and assess new technology in blood and marrow transplantation. Registry data will be critical for extrapolating results of these trials, which tend to be applied in restricted populations, to other patients, and for evaluating the impact of preparative regimens, demographic factors, prior treatment, and other variables on transplant outcome.

APPENDIX
Institutions That Report Breast Cancer Cases to the ABMTR

Country/Institution	City	Country/Institution	City
Argentina		Baptist Regional Cancer Center	Jacksonville, FL
Alexander Fleming Institute	Buenos Aires	University of Kansas Medical Center	Kansas City, KS
Centro de Internacion e Investigation	Buenos Aires	Scripps Clinic & Research Foundation	La Jolla, CA
Hospital Privado de Oncologia	Buenos Aires	Dartmouth-Hitchcock Medical Center	Lebanon, NH
Navy Hospital "Pedro Mallo"	Buenos Aires	University of Kentucky Medical Center	Lexington, KY
Hospital Privado de Cordoba	Cordoba	University of Arkansas for Health	
Austria		Sciences	Little Rock, AR
Donauspital	Vienna	UCLA Center for Health Sciences	Los Angeles, CA
Brazil		USC/Norris Cancer Hospital	Los Angeles, CA
Hospital de Clinicas	Curitiba	James Graham Brown Cancer Center	Louisville, KY
Hospital Nossa Senhora das Gracas	Curitiba	University of Wisconsin	Madison, WI

Canada
  University of Calgary   Calgary
  Royal Victoria Hospital   Montreal
  Sacré Coeur Hospital   Montreal
  Northeastern Ontario Regional Cancer
    Centre   Sudbury
  Toronto Hospital   Toronto
  Vancouver General Hospital   Vancouver
  Manitoba Cancer Treatment Center   Winnipeg
Cuba
  Hermanos Ameijeiras Hospital   Havana
Mexico
  Institute Nacional de Cancerologia   Mexico City
  Centro de Hematologia y Medicina
    Interna   Puebla
Russia
  Petrov Research Institute of Oncology   St. Petersburg
United States
  Presbyterian Health Care Services   Albuquerque, NM
  University of Michigan Medical Center   Ann Arbor, MI
  Arlington Cancer Center   Arlington, TX
  Emory Clinic   Atlanta, GA
  Southwest Regional Cancer Center   Austin, TX
  Johns Hopkins Hospital   Baltimore, MD
  University of Maryland Cancer Center   Baltimore, MD
  Mary Bird Perkins Cancer Center   Baton Rouge, LA
  Alta Bates Hospital   Berkeley, CA
  University of Alabama at Birmingham   Birmingham, AL
  Dana-Farber Cancer Institute   Boston, MA
  Montefiore Medical Center   Bronx, NY
  Roswell Park Cancer Institute   Buffalo, NY
  University of North Carolina Chapel Hill Chapel Hill, NC
  Medical University of South Carolina   Charleston, SC
  University of Virginia Medical Center   Charlottesville, VA
  Rush Presbyterian/St. Luke's Medical
    Center   Chicago, IL
  University of Chicago Medical Center   Chicago, IL
  Jewish Hospital of Cincinnati   Cincinnati, OH
  University Hospital Cincinnati   Cincinnati, OH
  Case Western Reserve University
    Hospital   Cleveland, OH
  Cleveland Clinic Foundation   Cleveland, OH
  University of South Carolina   Columbia, SC
  Ohio State University Hospital   Columbus, OH
  Baylor University Medical Center   Dallas, TX
  Miami Valley Hospital   Dayton, OH
  Presbyterian/St. Luke's Hospital   Denver, CO
  Wayne State University   Detroit, MI
  City of Hope National Medical Center   Duarte, CA
  University of Connecticut Health Center Farmington, CT
  Bone Marrow & Stem Cell Institute of   Fort Lauderdale,
    Florida   FL
  Harris Methodist Oncology Program   Fort Worth, TX
  University of Florida, Shands Hospital   Gainesville, FL
  East Carolina University School of
    Medicine   Greenville, NC
  Hackensack Medical Center   Hackensack, NJ
  Hinsdale Hematology-Oncology
    Associates   Hinsdale,
  Queen's Cancer Center   Honolulu, HI
  St. Francis Medical Center   Honolulu, HI
  Baylor College of Medicine   Houston, TX

  M.D. Anderson Cancer Center   Houston, TX
  Indiana University Hospital &
    Outpatient Center   Indianapolis, IN
  Methodist Hospital of Indiana   Indianapolis, IN
  St. Vincent Hospital & Health Care Ctr. Indianapolis, IN
  North Shore University Hospital   Manhasset, NY
  Marshfield Clinic   Marshfield, WI
  Loyola University Medical Center   Maywood, IL
  Methodist Hospital Central   Memphis, TN
  Baptist Hospital of Miami   Miami, FL
  Froedtert Memorial Lutheran   Milwaukee, WI
  St. Luke's Medical Center   Milwaukee, WI
  Abbott Northwestern Hospital   Minneapolis, MN
  University of Minnesota   Minneapolis, MN
  West Virginia University   Morgantown, WV
  Vanderbilt University Medical Center   Nashville, TN
  Columbia Presbyterian Medical Center   New York, NY
  Mount Sinai Medical Center   New York, NY
  Medical Center of Delaware   Newark, DE
  Hoag Cancer Center   Newport Beach, CA
  University of Oklahoma Health
    Sciences Center   Oklahoma City, OK
  University of Nebraska Medical Center   Omaha, NE
  Saint Joseph Hospital   Orange, CA
  Lutheran General Hospital   Park Ridge, IL
  Hematology Associates   Peoria, IL
  Hahnemann University Hospital   Philadelphia, PA
  Temple University Compehensive
    Cancer Center   Philadelphia, PA
  University of Pennsylvania Hospital   Philadelphia, PA
  Shadyside Hospital   Pittsburgh, PA
  University of Pittsburgh   Pittsburgh, PA
  Cancer Center of Boston   Plymouth, MA
  North Shore Hem/Onc Assoc   East Setauket, NY
  Oregon Health Sciences Univ.   Portland, OR
  Roger Williams Medical Center   Providence, RI
  Cancer & Blood Institute of the Desert   Rancho Mirage, CA
  Washow Regional Cancer Center   Reno, NV
  Mayo Clinic Rochester   Rochester, NY
  University of Rochester   Rochester, NY
  Sutter Memorial Hospital   Sacramento, CA
  University of California Davis Cancer
    Center   Sacramento, CA
  Latter Day Saints Hospital   Salt Lake City, UT
  University of Utah Medical Center   Salt Lake City, UT
  South Texas Cancer Institute   San Antonio, TX
  University of Texas Health Sciences
    Center   San Antonio, TX
  University of CA, San Diego   San Diego, CA
  University of CA, San Francisco
    Medical Center   San Francisco, CA
  Mayo Clinic Scottsdale   Scottsdale, AZ
  LSU Medical Center-Shreveport   Shreveport, LA
  Memorial Medical Center   Springfield, IL
  Tufts University School of Medicine   Springfield, MA
  Methodist Hospital/Nicollet Cancer
    Center   St. Louis Park, MN
  St. Louis University Medical Center   St. Louis, MO
  Bennett Cancer Center   Stanford, CT
  Stanford University Hospital   Stanford, CA
  SUNY-Health Science Center   Syracuse, NY

H. Lee Moffitt Cancer Center	Tampa, FL	Walter Reed Army Medical Center	Washington, DC
Arizona Cancer Center	Tucson, AZ	Westlake Comprehensive Cancer Center	Westlake Village, CA
St. Francis Hospital	Tulsa, OK	St. Francis Hospital	Wichita, KS
New York Medical College	Valhalla, NY	Wake Forest University	Winston-Salem, NC
George Washington University Medical		University of Massachusetts Medical	
Center	Washington, DC	Center	Worcester, MA

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FACTORS CORRELATED WITH PROGRESSION-FREE SURVIVAL AFTER HIGH-DOSE THERAPY AND HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR METASTATIC BREAST CANCER

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ABSTRACT

Context.-Women with breast cancer are the most frequent recipients of high-dose therapy followed by autologous hematopoietic stem cell transplantation (autotransplants) in North America. Despite widespread use there remains controversy about who are most appropriate candidates.

Objective.-To determine factors correlated with progression-free survival after autotransplant in women with metastatic breast cancer.

Design.-Cohort study; Cox regression analysis of observational database.

Setting.-63 North American hospitals between 1989 and 1995.

Participants.-1188 consecutive women aged 18 to 70 years receiving autotransplants for metastatic or locally recurrent breast cancer.

Main Outcome Measures.-Time to treatment failure (progression or death) from time of autotransplant.

Results.-Three-year probabilities of survival and progression-free survival were 31 (28-34)% and 13 (10-16)%. Factors associated with significantly (p<0.05) increased risk of treatment failure were: age > 45 yrs; Karnofsky performance score < 90%; absence of hormone receptors; prior use of adjuvant chemotherapy; initial disease-free survival interval with adjuvant treatment ≤18 months; metastases in the liver or central nervous system (compared to soft tissue, bone or lung); 3 or more sites of metastatic disease; and incomplete or no response (compared to a complete response) to standard dose chemotherapy. Receiving hormonal therapy posttransplant was associated with a reduced risk of treatment failure in women with hormone receptor positive tumors (p=0.0001).

Conclusion.-These data indicate some women are very unlikely to benefit from autotransplant and should only receive this treatment in the context of clinical trials attempting to improve outcome.

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INTRODUCTION

Metastatic or locally recurrent breast cancer is generally an incurable disease (1). High-dose

therapy followed by autologous hematopoietic stem cell transplantation (autotransplant) is an

increasingly used treatment approach for this disorder. Breast cancer is the most common

indication for hematopoietic stem cell transplantation in North America and most women

receiving autotransplants have advanced disease (2). Despite widespread use, its appropriateness

and benefits are still debated (3-5). Many phase I and II studies report outcomes of

autotransplants in women with advanced breast cancer (6-17) and one published randomized trial

compares standard to high-dose therapy (18). Inclusion criteria for these studies differ and

numbers of subjects are usually small. We recently reported data from 3,500 women with

advanced breast cancer treated at centers reporting to the Autologous Blood and Marrow

Transplant Registry (ABMTR) (2). Three-year progression-free survival (PFS) ranged from 7-

32% depending on response to conventional dose chemotherapy prior to autotransplant.

Identifying women most likely to benefit from autotransplants for advanced breast cancer is

important for women and doctors deciding treatment options and for investigators developing

new trials. Factors predicting treatment failure after conventional therapy are reasonably well-

established (19-25). Few multivariate analyses of such factors are published for women receiving

autotransplants (13, 15, 16). We studied 1188 women with advanced (metastatic or locally

recurrent) breast cancer receiving autotransplants at 63 centers to determine factors associated

with progression or death (treatment failure).

METHODS

Data Collection

The ABMTR is a voluntary organization of more than 200 institutions performing autotransplants, primarily in the United States, Canada, and Central and South America. Centers report data on consecutive autotransplants to a Statistical Center at the Medical College of Wisconsin. The ABMTR defines autotransplant as treatment with a sufficiently high dose of chemotherapy to warrant autologous bone marrow- or blood-derived hematopoietic stem cell support.

The ABMTR began data collection in 1992. Data were collected retrospectively for women receiving autotransplants between 1989 and 1992 and prospectively thereafter. Participating centers register consecutive autotransplants for all disease indications. Based on data collected in the Centers for Disease Control Hospital Surveys (26,27), about half of autotransplants in North America are registered with the ABMTR.

The ABMTR collects data at two levels: Registration and Research. Registration data include disease type, age, sex, pretransplant disease stage and chemotherapy-responsiveness, date of diagnosis, graft type (bone marrow- and/or blood-derived stem cells), high-dose conditioning regimen, posttransplant disease progression and survival, development of a new malignancy and cause of death. Requests for data on progression or death for registered patients are at six month intervals. All ABMTR teams contribute Registration data. Research data is collected on subsets of registered patients, including comprehensive pre- and posttransplant clinical information such as tumor size and pathology, sites of disease, menopausal status, hormone receptor status, all breast cancer treatments before and after transplant, clinical status (including cardiac, pulmonary, renal and liver function) before and after transplant, doses of high-dose therapy, and blood or

marrow graft treatment and sites of posttransplant progression.

Patients

This analysis uses ABMTR Research data reported for 1188 women with metastatic and locally recurrent breast cancer consecutively transplanted by 63 teams between January 1, 1989 and January 31, 1995 (Participating centers listed in Appendix.). Women with disease recurrence solely in the contralateral breast were excluded because of difficulty in distinguishing recurrence from a new primary site of disease. One hundred and seven women were excluded because of incomplete data for sites of metastases or date of diagnosis of metastatic disease. The survival of women excluded was not different from the 1188 included in the analysis (log-rank test for difference in survival probability p=0.58). Women were considered to have hormone receptor positive tumors if either estrogen receptor (ER) or progesterone receptor (PR) assays were positive; those reported as having borderline receptor levels were grouped with the receptor-negative patients. Women in whom metastases were found within one month of diagnosis of breast cancer were considered in the same group as women with metastases at first presentation. Women with pleural or parenchymal lung disease were considered as a single group.

Statistical Methods

The primary outcome was treatment failure, the inverse of PFS. Events were death, progression, and, in women with a complete response, breast cancer recurrence. Women alive without progression or recurrence were censored at last follow-up. Univariate probabilities of survival and PFS were calculated using the Kaplan-Meier estimator. Variables were tested in univariate analysis for their association with treatment failure using Cox proportional hazards regression; these analyses also examined whether the proportional hazards assumption was met, using the time-dependent covariate method. Optimal cut points for categorizing continuous

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variables were determined using Martingale residual plots (28). A forward stepwise selection method with a significance level of 0.05 was used to select variables for the multivariate model. All analyses were performed using PROC PHREG in SAS® version 6.12. Covariates in the final multivariate model were tested for proportional hazards, using the time-dependent covariate method, and for first order interactions. Tests for "center effects" (inter-center differences unexplained by known covariates) were not statistically significant (29).

Posttransplant hormone and radiation therapy: Studying effects of posttransplant maneuvers on outcome, such as posttransplant hormone therapy and radiation therapy, must account for bias introduced by early deaths occurring before intended treatments were administered. This bias artificially increases the proportion of adverse events in the non-treatment group if all patients are considered from the time of transplant. This bias was overcome by only studying effects of posttransplant hormone and radiation therapy in women already surviving without disease recurrence more than 6 months posttransplant. Hormone therapy was analyzed in 4 groups; women who were hormone receptor positive and received therapy pretransplant only, posttransplant only, both pre- and posttransplant and those receiving hormone therapy neither pre- or posttransplant. These 4 groups were compared simultaneously against women with hormone receptor negative tumors while adjusting for other variables found to be significant in the multivariate analyses. Prophylactic posttransplant radiation therapy was similarly studied in women surviving > 6 months posttransplant.

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RESULTS

The distribution of patient-, disease- and transplant-related characteristics of the 1188 women are presented in Table 1. Median follow-up after transplant was 29.5 months. The three-year probabilities of survival and PFS were 31 (28-34)% and PFS 13 (10-16)%, respectively (Figure 1).

Univariate analyses

Eight factors were significant (p<0.001) and four marginally significant (p<0.05-0.01) in univariate analyses of association with treatment failure. Significant variables were breast cancer stage at diagnosis, hormone receptor status, use of adjuvant chemotherapy, initial disease-free interval, response to pretransplant chemotherapy, pretransplant Karnofsky performance score, and number and sites of metastases. Marginally significant variables were age, use of radiation therapy prior to transplant, type of high-dose therapy used and year of transplant.

Multivariate analysis

Factors significant in the final multivariate model of risk of treatment failure are shown in Table 2. All highly significant variables from the univariate analyses remained significant in the final model (see Methods). Of the marginally significant variables only age remained in the model. Women older than 45 years at time of transplant had relative risk (RR) of treatment failure of 1.17 (95% confidence interval, 1.02, 1.33) compared with younger women (p=0.02). A low Karnofsky performance score pretransplant (<90%) was associated with an increased risk of treatment failure 1.27 (1.07, 1.51), (p<0.005). Absence of hormone receptors was associated with a RR of treatment failure of 1.31(1.15, 1.51) compared to women with hormone receptor positive tumors (p<0.0001).

A complex interaction was found between prior use of adjuvant chemotherapy and initial disease-free interval (interval from diagnosis of breast cancer to detection of metastatic disease). First, women whose first presentation was with metastatic disease were not eligible for adjuvant therapy. Additionally, the effect of prior adjuvant therapy on posttransplant treatment failure differed in women with initial disease-free intervals ≤ and > 18 months. These two variables were therefore combined in the final model into a single covariate with the following categories: metastatic breast cancer at diagnosis, no adjuvant therapy, adjuvant therapy and disease-free interval ≤ 18 months, adjuvant therapy and disease-free interval > 18 months. Women not receiving adjuvant therapy had the same risk of treatment failure as women with metastases at diagnosis. Disease-free interval was not significant in women not receiving adjuvant chemotherapy. Women receiving adjuvant chemotherapy with a disease-free interval ≤ 18 months had a high risk of treatment failure (RR 1.99 [1.62, 2.43], p<0.0001) as did women receiving adjuvant chemotherapy with a disease-free interval > 18 months (RR 1.31 [1.10, 1.56], p=0.002). The latter two groups were also significantly different from each other (p<0.001).

Number and sites of metastases were also important. Four important prognostic groups were determined in the final model. Women with one or two sites of metastases, providing neither were viscera (other than lung) or central nervous system (CNS), had similar risks of treatment failure and were used as the reference group. Women with CNS or liver metastases or metastases in three or more organs of any kind had a poor prognosis.

Risk of treatment failure correlated strongly with pretransplant response to chemotherapy. Women with a partial response to chemotherapy had a RR of 1.65 (1.36, 1.99) (p<0.0001), and women with resistant disease a RR of 1.87 (1.54, 2.27) (p<0.0001) compared to women in complete remission, but were not significantly different from each other (p=0.09). Women with

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indeterminant sensitivity (due to bone only disease, single site disease excised or irradiated pretransplant, or response to chemotherapy untested) had a RR of treatment failure similar to the reference group. Figures 2-4 present Kaplan-Meier estimates of PFS according to chemotherapy sensitivity pretransplant, number and sites of metastases, adjuvant chemotherapy and disease-free interval.

Posttransplant Hormone and Radiation Therapy

Effect of posttransplant hormone therapy was only analyzed in women surviving without progression six months posttransplant. After adjustment for other variables in the final model described above, posttransplant hormone therapy was associated with decreased treatment failure in women with hormone receptor positive disease. Use of pretransplant hormone therapy did not influence posttransplant PFS regardless of whether posttransplant hormones were given. The use of radiation as part of the planned posttransplant treatment was not associated with improved outcome (Table 3).

DISCUSSION

In this study of 1188 women receiving autotransplants for advanced breast cancer, use of posttransplant hormonal therapy in women with hormone receptor positive tumors significantly reduced risk of treatment failure. Eight other factors were significant predictors of treatment failure in multivariate analysis, including age >45 years; Karnofsky performance score <90; CNS or liver metastases or metastases involving three or more sites; hormone receptor negative tumors; use of adjuvant chemotherapy; initial disease-free interval ≤ 18 months in women receiving adjuvant chemotherapy; and poor response to chemotherapy pretransplant. Surprisingly, there was little difference in risk of treatment failure between women with partial and no response to chemotherapy pretransplant. From this study it is not possible to state

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whether conventional dose therapy affected the natural history of the disease or just identified

women who would do poorly with autotransplant.

The survival of women with advanced breast cancer varies widely, regardless of treatment

given. Prior studies attempting to define patient, disease and treatment factors predicting

progression or death following therapy are summarized in Table 4 (8,13,15,16,19-25,30).

Interpretation of these studies and their sometimes conflicting results is difficult. Variations

among studies likely relate to small sizes of study populations and differing selection criteria.

Additionally, in most studies statistical techniques did not attempt to adjust for important

interactions between factors and changes in effect of factors over time as was done in the current

analysis (28). This study analyzed a large population of women consecutively transplanted,

examined interactions among factors under study and considered changing effects of factors on

treatment failure over time. Women receiving autotransplants are no doubt a selected group of

women with advanced breast cancer, however we believe this study accurately determines factors

affecting outcome of women receiving this therapy.

There are several important negative findings from this study. Interval from diagnosis of

metastases to transplant, prior hormonal therapy, prior anthracycline therapy, use of growth

factors to enhance marrow recovery; and source of stem cells did not affect progression-free

survival. Several factors were significantly correlated with treatment failure in univariate analysis

but not after adjustment for other prognostic factors in multivariate analysis. These included

stage of breast cancer at diagnosis, prior radiation therapy, high-dose therapy regimen and

calendar year. Correlations among variables may account for some differences in published

studies. Outcomes were similar among the 63 teams contributing data, after adjustment for patient

characteristics.

The only intervention found to reduce treatment failure after autotransplant was the use of hormone therapy after transplant. This should therefore be recommended in all hormone receptor positive women. Failure to determine a superior high-dose chemotherapy regimen suggests that women should be treated with the least toxic transplant regimens (unless volunteering to be part of a clinical trial). Absence of an effect on treatment failure of interval from diagnosis of metastases to transplant in this study may indirectly support a recently reported benefit on survival of delaying autotransplant until progression of disease in women achieving a complete remission after standard dose chemotherapy (30).

The question of superiority of high-dose compared with standard dose therapy for advanced breast cancer is not addressed by this study. However, the data suggest that some women are very unlikely to benefit from this approach: women with resistant disease, CNS metastases, three or more metastatic sites and those who relapsed early after adjuvant chemotherapy for early stage disease all had PFS rates of <10% at three years (Figures 2-4). Such women should probably not be considered for autotransplants except in the context of clinical trials designed to test regimens that might improve this very poor prognosis.

In this study of a large number of women consecutively treated with autotransplants for advanced breast cancer, we determined patient-, disease- and transplant-related factors associated with treatment failure. The large number and complex interaction of prognostic factors determined in this study highlight the need for careful statistical analyses on large numbers of patients to determine prognostic factors and impact of new therapies in treating women with advanced breast cancer. The design of new clinical trials should consider data available in information resources such as the ABMTR and similar organizations.

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Table 1.   Patient-, disease- and treatment-related factors and their association with risk of treatment failure (progression or death) in univariate analyses.

Variable	N (%)	RR (95% CI)	P-value
Age at transplant			
Median (range), years	44 (18-70)		
≤ 45 years	658 (55%)	1.00	---
> 45 years	530 (45%)	1.15 (1.01,1.31)	0.036
Stage *at diagnosis*			0.0004
Metastatic	221 (19%)	1.00	---
Stage I[a]	98 (8%)	1.02 (0.76,1.36)	0.91
Stage II[a]	377 (32%)	1.26 (1.03,1.55)	0.02
Stage III (includes inflammatory)[a]	94 (8%)	1.63 (1.23,2.16)	0.0006
Not metastatic, initial stage unknown[a]	398 (33%)	1.42 (1.17,1.73)	0.0004
Initial surgery type			0.41
Lumpectomy	269 (22%)	0.91 (0.77,1.08)	0.26
Mastectomy	835 (70%)	1.00	---
None[b] (N=63) or unknown (N=21)	84 (7%)	1.08 (0.84,1.39)	0.56
Hormone receptor status			0.0005
Positive	676 (57%)	1.00	---
Not tested (N=60) or unknown (N=42)	102 (9%)	1.14 (0.79,1.64)	0.47
Negative / borderline	410 (35%)	1.28 (1.12,1.47)	0.0003
Interval from diagnosis to metastases			<0.0001
Median (range), months	21 (0-238)		
Metastatic disease at diagnosis	221 (19%)	1.00	---
≤ 18 months[a]	312 (26%)	1.72 (1.40,1.32)	<0.0001
> 18 months[a]	655 (55%)	1.32 (1.10,1.58)	0.003
Response to pretransplant chemotherapy			<0.0001
Complete response	263 (23%)	1.00	---
Partial response	375 (33%)	1.71 (1.42,2.06)	<0.0001
Resistant	330 (29%)	2.07 (1.72,2.05)	<0.0001
Indeterminant / untested	169 (15%)	1.18 (0.94,1.49)	0.16
Missing	51	1.13 (0.92,1.94)	0.12
Karnofsky score pretransplant			<0.0001
90-100%	895 (75%)	1.00	---
< 90%	214 (18%)	1.44 (1.22,1.69)	0.0001
Unknown	79 (7%)	1.48 (1.15,1.91)	0.003

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Table 1, continued

Variable	N (%)	RR (95% CI)	P-value
Interval from metastases to transplant			
Median (range), months	8 (<1-138)	1.00 (0.99,1.01)	0.11
Sites of metastases pretransplant			0.0001
Bone/Bone marrow only	207 (17%)	1.00	---
Lung only	76 (6%)	1.25 (0.92,1.69)	0.16
Liver only	62 (5%)	1.66 (1.21,2.28)	0.002
Soft tissue only	262 (22%)	1.22 (0.98,1.51)	0.07
CNS ± other	21 (2%)	2.25 (1.41,3.39)	0.0007
Bone + lung	50 (4%)	1.54 (1.09,2.16)	0.01
Bone + liver	34 (3%)	1.88 (1.25,2.82)	0.002
Bone + soft tissue	96 (8%)	1.18 (0.89,1.56)	0.25
Lung + soft tissue	59 (5%)	1.49 (1.08,2.07)	0.016
Other 2 sites[c]	40 (3%)	2.52 (1.76,3.60)	<0.0001
Bone + lung + soft tissue	35 (3%)	3.00 (2.05,4.37)	<0.0001
Other 3 sites[d]	45 (4%)	2.13 (1.50,3.03)	<0.0001
4 or more sites + other visceral[e]	201 (17%)	1.44 (1.15,1.79)	0.0014
Radiation therapy pretransplant			
No	574 (48%)	1.00	---
Yes	614 (52%)	1.18 (1.04,1.36)	0.01
Hormone therapy pretransplant			
No	609 (51%)	1.00	---
Yes	579 (49%)	0.99 (0.88,1.13)	0.96
Anthracyclines pretransplant[f,g]			
No	203 (17%)	1.00	---
Yes	985 (83%)	1.02 (0.86,1.21)	0.80
Adjuvant chemotherapy given			<0.0001
No adjuvant chemotherapy[h]	220 (19%)	1.00	---
Metastases at diagnosis[i]	221 (19%)	0.94 (0.76,1.16)	0.55
CMF ± other[j]	357 (31%)	1.46 (1.22,1.75)	<0.0001
CAF ± other[k]	197 (18%)	1.55 (1.26,1.90)	<0.0001
Other chemotherapy	143 (13%)	1.70 (1.34,2.17)	<0.0001

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Table 1, continued

Variable	N (%)	RR (95% CI)	P-value
Conditioning regimen, N evaluable	1184		0.04
CyTCb	311 (26%)	1.00	---
CyT	143 (12%)	1.16 (0.93,1.44)	0.20
CyTM	48 (4%)	0.92 (0.63,1.34)	0.67
ICE	70 (6%)	1.19 (0.89,1.57)	0.24
CyCbM	30 (3%)	1.24 (0.83,1.87)	0.29
CyTHu	106 (9%)	1.01 (0.79,1.30)	0.93
CyCbE	67 (6%)	1.16 (0.86,1.56)	0.33
CyCisE	45 (4%)	1.64 (1.17,2.29)	0.004
MT	63 (5%)	1.57 (1.17,2.29)	0.003
CyMVnb	30 (3%)	1.33 (0.88,2.00)	0.18
Other with BCNU	36 (3%)	0.89 (0.59,1.33)	0.56
Other no BCNU	235 (20%)	1.20 (0.99,1.46)	0.06
G/GM - CSF in first 7 days, N evaluable	1155		
No	278 (24%)	1.00	---
Yes	877 (76%)	0.90 (0.78,1.05)	0.19
Source of graft			0.30
Bone marrow	463 (39%)	1.00	---
PBSC	507 (43%)	0.98 (0.85,1.13)	0.78
Bone marrow + PBSC	218 (18%)	0.13 (0.94,1.35)	0.20
Year of transplant			0.08
1989-1990	201 (17%)	1.00	---
1991-1992	475 (40%)	0.88 (0.74,1.05)	0.16
1993-1995	512 (43%)	0.81 (0.68,0.97)	0.02

Abbreviations: RR = relative risk; CI = confidence interval; CNS=central nervous system; C = cyclophosphamide; M = methotrexate; F = 5-flurouracil; A = adriamycin; Cy = cyclophosphamide; T = thiotepa; Cb = carboplatin; M=Mitoxantrone; ICE = ifosphamide, carboplatin and etoposide; Hu = hydroxurea; E = etoposide; Cis =cisplatin; Vnb = vinblastine; BCNU = carmustine; G = granulocyte; GM = granulocyte-macrophage; CSF = colony-stimulating factor; PBSC = peripheral blood stem cells

Footnotes
[a] These women had Stage I, II or III disease at diagnosis, may or may not have received adjuvant therapy, and subsequently developed metastases.
[b] These women received chemotherapy prior to surgery.
[c] Other 2 sites include: lung + liver; liver + soft tissue.
[d] Other 3 sites include: bone + lung + liver; bone + liver + soft tissue; lung + liver + soft tissue.
[e] Other viscera includes visceral sites other than lung, liver or CNS.
[f] Includes adriamyacin, mitoxantrone, and epirubicin.

Table 1, Footnotes, *continued.*

[g] Dose of anthracycline also tested and not significant (p=0.86)

[h] Refers only to women with Stage I-III disease at diagnosis.

[i] These women not eligible for adjuvant chemotherapy.

[j] Excludes anthracyclines

[k] Excludes methotrexate

Table 2. Multivariate analysis of treatment failure in 1188 women with metastatic breast cancer receiving autologous transplants between January 1, 1989, and January 31, 1995, at 63 centers in North America and reported to the ABMTR.

Covariates	RR	95% CI	P-value
Age at transplant			
≤ 45 years	1.00		---
> 45 years	1.17	(1.02,1.33)	0.02
Karnofsky score, pretransplant			0.0008[a]
90-100%	1.00		---
< 90%	1.27	(1.07, 1.51)	0.005
Hormone receptor status			
Positive	1.00		---
Negative	1.31	(1.15, 1.51)	0.0001[b]
Adjuvant chemotherapy and DFI			0.0001[a]
None given[c]	1.00		---
Metastatic disease at diagnosis	0.96	(0.78, 1.19)	0.71[b]
Chemotherapy given and DFI ≤ 18 months[c]	1.99	(1.62, 2.43)	0.0001[b]
Chemotherapy given and DFI > 18 months[c]	1.31	(1.10, 1.56)	0.002[b]
Sites of metastatic disease, pretransplant			0.0001[a]
Not liver or CNS, 1-2 sites[d]	1.00		---
CNS ± other	1.56	(0.99, 2.46)	0.05[b]
Liver, 1-2 sites[e]	1.47	(1.20, 1.80)	0.0002[b]
3+ sites[f]	1.32	(1.13, 1.54)	0.0005[b]
Chemotherapy sensitivity pretransplant			0.0001[a]
Complete remission	1.00		---
Partial remission	1.65	(1.36, 1.99)	0.0001[b]
Resistant	1.87	(1.54, 2.27)	0.0001[b]
Indeterminant / unknown	1.20	(0.97, 1.50)	0.10[b]

Abbreviations: RR = relative risk; CI = confidence interval; DFI = disease-free interval; CNS = central nervous system

[a] Overall p-value for effect of the categorical covariate using the Wald test.
[b] P-value for pairwise comparisons of specific category with the reference (baseline) group
[c] Refers to women with Stage I-III disease at diagnosis, who subsequently developed metastases.
[d] Not liver or CNS (1-2 sites) includes: bone; bone marrow; soft tissue; lung; bone + lung; bone + soft tissue; lung + soft tissue.
[e] Liver (1-2 sites) includes: liver, bone + liver; lung + liver; liver + soft tissue
[f] 3+ sites includes: bone + lung + liver; bone + liver + soft tissue; bone + lung + soft tissue; lung + liver + soft tissue; 4+ sites; other viscera (excluding liver, lung and CNS)

Table 3. Effect of posttransplant hormonal therapy and radiation in 999 patients surviving 6 months after autotransplant for advanced breast cancer.

Covariate	N	RR	P
Hormone receptor status		-	0.0004
Negative	358	1.00	--
Positive-no hormone therapy[a]	517	0.87 (0.74, 1.01)	0.07
Positive-hormone therapy[a]	124	0.60 (0.41, 0.87)	0.0001
No planned posttransplant radiation	832	1.00	--
Planned posttransplant radiation	167	0.94 (0.77, 1.16)	0.59

Abbreviations: RR = relative risk

[a] Pairwise comparison p=0.003

Table 4. Factors associated with increased risk of progression or death in prior studies of women with advanced breast cancer treated with standard dose chemotherapy or autotransplant.

Chemotherapy Studies	Autotransplant studies	ABMTR multivariate analysis
Age < 45 yrs (22) Age < 50 yrs (20) Age > 50 yrs (24)	Age < 40 years (15)	Age > 45 years
ER-negative status (22,23)	ER-positive status (15)	Hormone receptor status-negative
DFI < 2 years (25)	DFI < 1 year (13) DFI < 2 years (15)	DFI ≤ 18 months if received adjuvant therapy
Adjuvant therapy (21,23) Prior radiation therapy (19) Failure of hormonal therapy (19) Delay of chemotherapy following oophorectomy (22)	Prior adjuvant therapy (13) Prior adriamycin therapy (16)	Adjuvant therapy
Extent of disease (19) Number of different sites >2 (20) Lung involvement (20) Liver involvement (20, 23) Visceral involvement (22) Soft tissue involvement (22)	Number of different sites > 1 (15) Number of different sites > 2 (8, 13) Liver involvement (8, 13) Soft tissue involvement (8, 13) Lung and/or liver metastases (16)	Number of different sites >2, if not liver or CNS Liver or CNS metastases
Poorer performance status (19)	------	
--------	Not achieving prior CR (15)	Karnofsky performance score < 90

--------	Early transplant after CR (30)	PR or Resistant disease .
	-------	-------
		No posttransplant hormonal therapy

Abbreviations: ER = estrogen receptor; DFI = disease-free interval; PR = partial response; CR = complete response

Appendix. Institutions reporting breast cancer cases to the ABMTR.

USA

Emory Clinic	Atlanta
Johns Hopkins Oncology Center	Baltimore
University of Maryland Cancer Center	Baltimore
Alta Bates Medical Center, Comprehensive Cancer Center	Berkeley
University of Alabama at Birmingham (UAB)	Birmingham
Dana-Farber Cancer Institute	Boston
Roswell Park Cancer Institute	Buffalo
University of North Carolina, Chapel Hill	Chapel Hill
Medical University of South Carolina	Charleston
St. Luke's Medical Center	Chicago
University of Chicago Medical Center	Chicago
The Jewish Hospital of Cincinnati	Cincinnati
University Hosp of Cleveland, Ireland Cancer Center	Cleveland
Baylor University Medical Center	Dallas
Miami Valley Hospital	Dayton
Presbyterian St. Lukes Hospital	Denver
Klabzuba Cancer Center	Fort Worth
University of Florida, Shands Hospital	Gainesville
Hackensack Medical Center	Hackensack
Baylor College of Medicine	Houston

Appendix, continued.

Indiana University Medical Center & Outpatient Center	Indianapolis
Methodist Hospital of Indiana	Indianapolis
University of Kansas Medical Center	Kansas City
University of California, San Diego	La Jolla
Dartmouth-Hitchcock Medical Center	Lebanon
UCLA Center for Health Sciences	Los Angeles
University of Louisville	Louisville
University of Wisconsin Hospital & Clinics	Madison
Methodist Hospital Central	Memphis
Baptist Hospital of Miami	Miami
Medical College of Wisconsin	Milwaukee
St. Luke's Medical Center	Milwaukee
Abbott Northwestern Hospital	Minneapolis
University of Minnesota Hospitals and Clinics	Minneapolis
West Virginia University Hospitals	Morgantown
Vanderbilt University Medical Center	Nashville
Medical Center of Delaware	Newark
University of Oklahoma Health Sciences Center	Oklahoma
CityUniversity of Nebraska Medical Center	Omaha
Lutheran General Hospital	Park Ridge
University of Pittsburgh Medical Center	Pittsburgh

Appendix, continued.

Cancer Center of Boston	Plymouth
Sutter Cancer Center	Sacramento
University of California, Davis Cancer Center	Sacramento
University of Utah Medical Center	Salt Lake City
University of Texas, Health Science Center at San Antonio	San Antonio
University of California, San Francisco	San Francisco
Louisiana State University Medical Center-Shreveport	Shreveport
Memorial Medical Center	Springfield
St. Louis University	St. Louis
Methodist Hospital & Park Nicollet Cancer Center	St. Louis Park
University Hospital-SUNY Health Sciences Center	Syracuse
H. Lee Moffitt Cancer Center	Tampa
St. Francis Hospital	Tulsa
Walter Reed Army Medical Center	Washington
St. Francis Hospital	Wichita
North Carolina Baptist Hospital/Bowman Gray School of Medicine	Winston-Salem

CANADA

Royal Victoria Hospital	Montreal
Sacre Coeur Hospital	Montreal
Northeastern Ontario Regional Cancer Center	Sudbury

Appendix, continued.

OTHER COUNTRIES

Hospital de Clinicas	Curitiba, Brazil
Centro de Hematologia y Medicina Interna	Puebla, Mexico
Petrov Research Institute of Oncology	St. Petersburg, Russia

LEGENDS FOR FIGURES

Figure 1.   Kaplan-Meier estimate of overall survival and progression-free

survival following autotransplant for 1188 women with metastatic

breast cancer tranplanted at 63 centers reporting to the ABMTR,

from 1989 to 1995.

Figure 2.   Kaplan-Meier estimates of progression-free survival by

chemotherapy sensitivity pretransplant. CR = complete remission;

PR = partial remission; IND/UNK = indeterminant/unknown.

Figure 3.   Kaplan-Meier estimates of progression-free survival women with

central nervous system (CNS), liver metastases or any disease at 3

or more sites.

Figure 4.   Kaplan-Meier estimates of progression-free survival for women

receiving no adjuvant chemotherapy (Adj chemo), receiving

adjuvant chemotherapy with a disease-free interval (DFI) $\leq$ 18

months and with a DFI > 18 months. Mets = metastases.

PROBABILITY OF PFS, %

YEARS

3 + sites (N : 281)

Liver 1-2 sites (N : 136)

Non-liver 1-2 sites (N : 750)

CNS (N : 21)

Figure showing a Kaplan-Meier plot of PROBABILITY OF PFS, % (y-axis, 0 to 100) versus YEARS (x-axis, 0 to 4). Curves labeled: Adj chemo, DFI >18 mos (N : 468); None given (N : 220); Mets at diagnosis (N : 221); Adj chemo, DFI ≤18 mos (N : 229). The word CONFIDENTIAL appears overlaid on the plot.
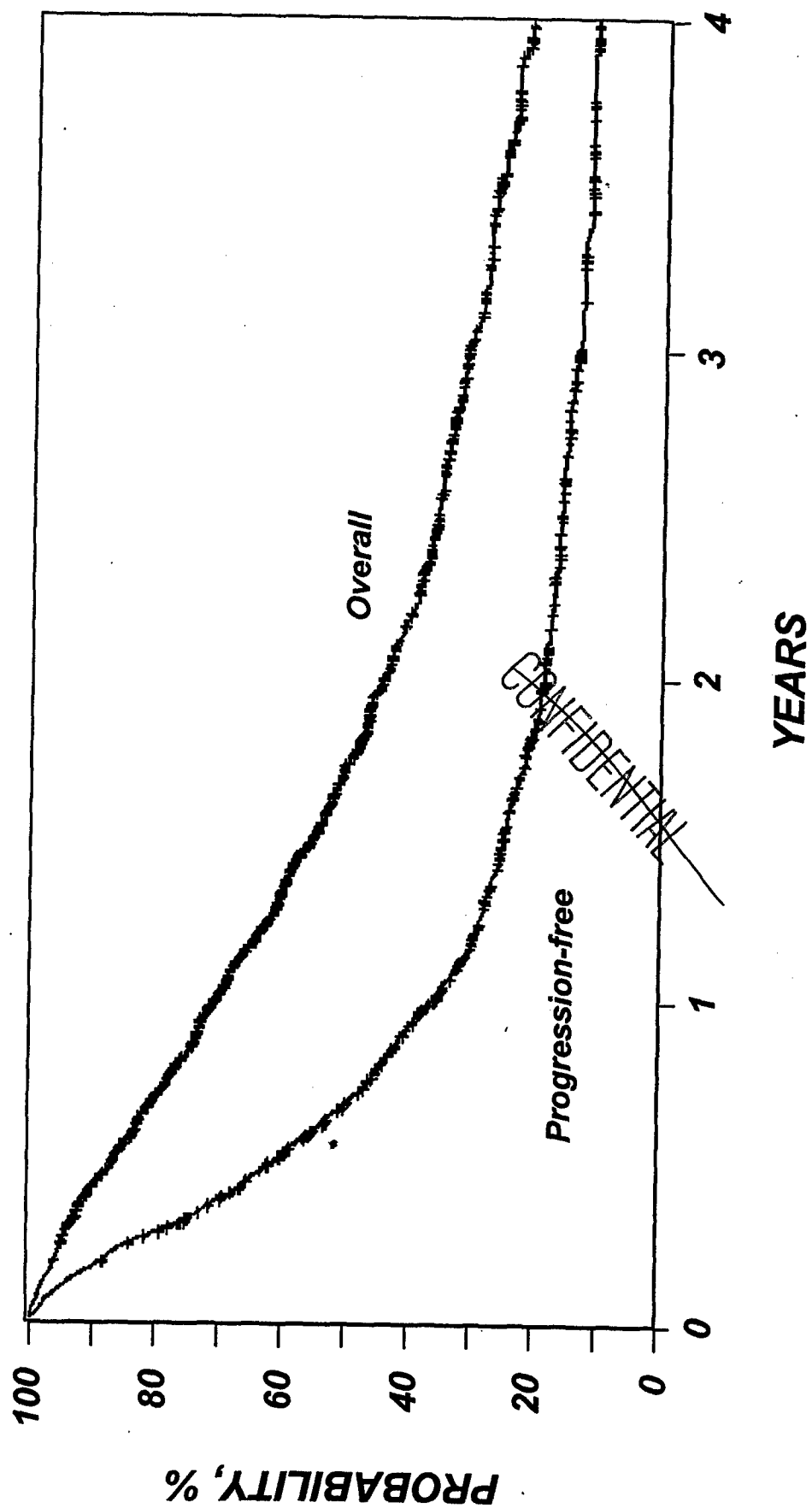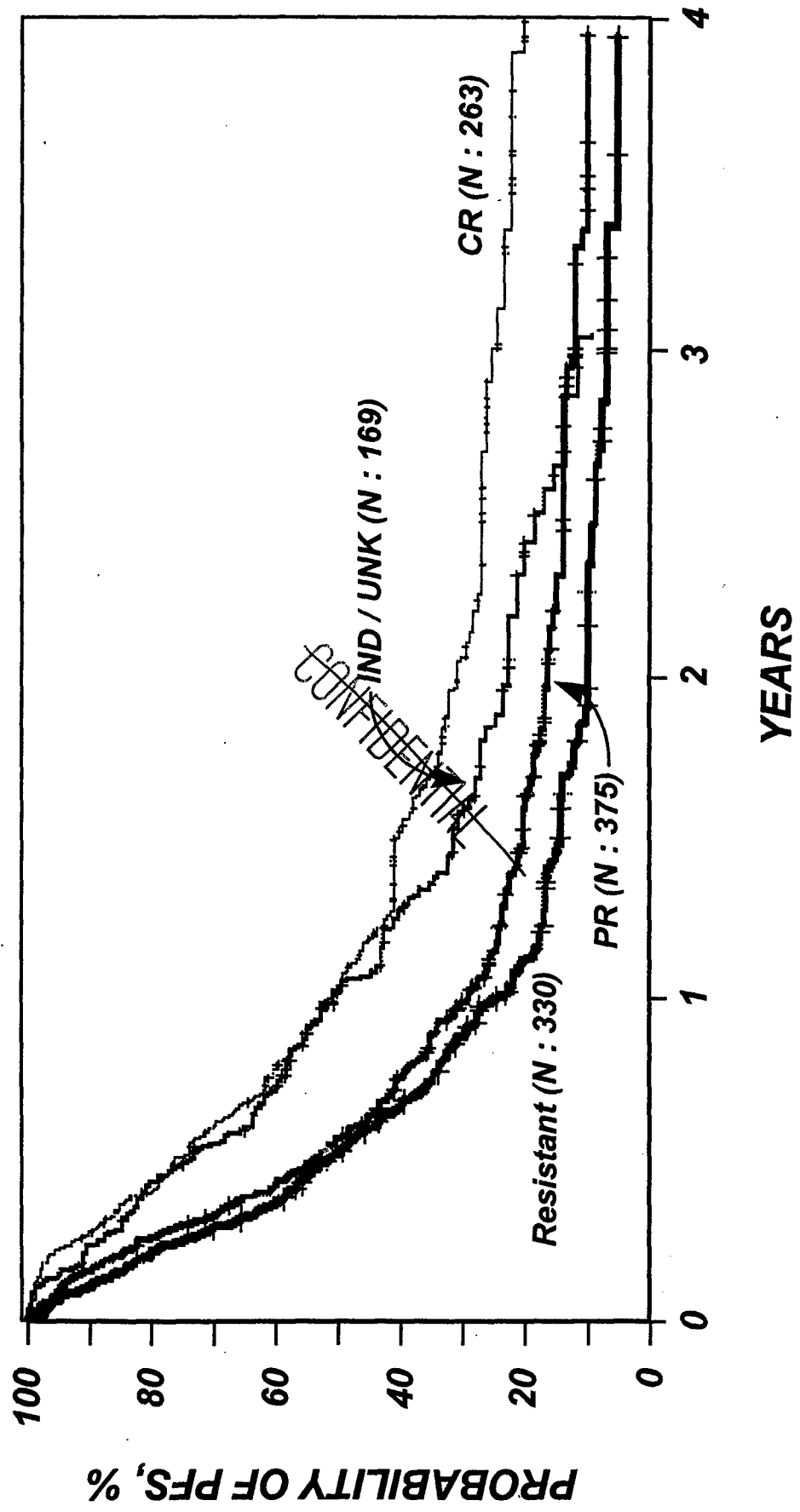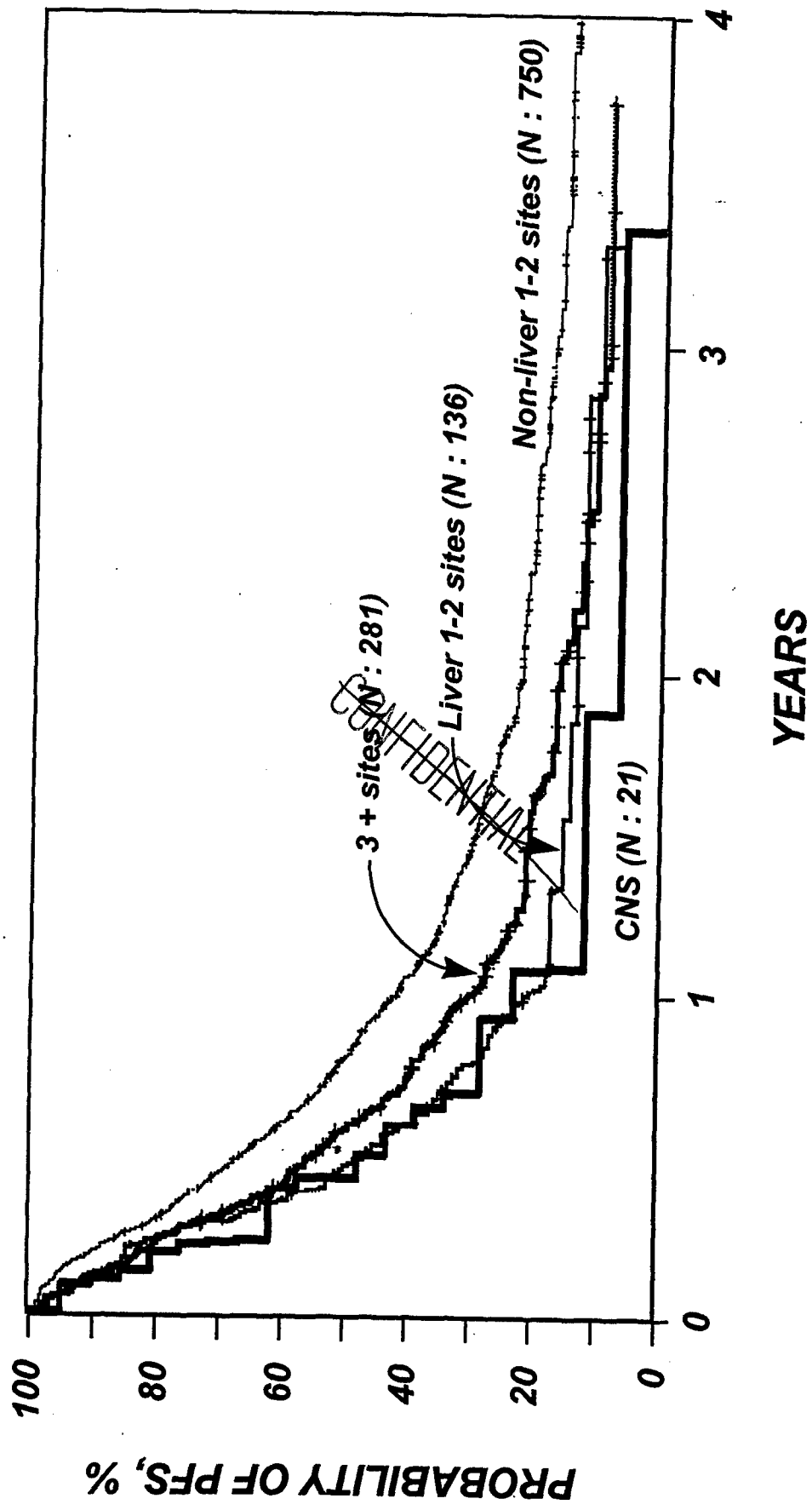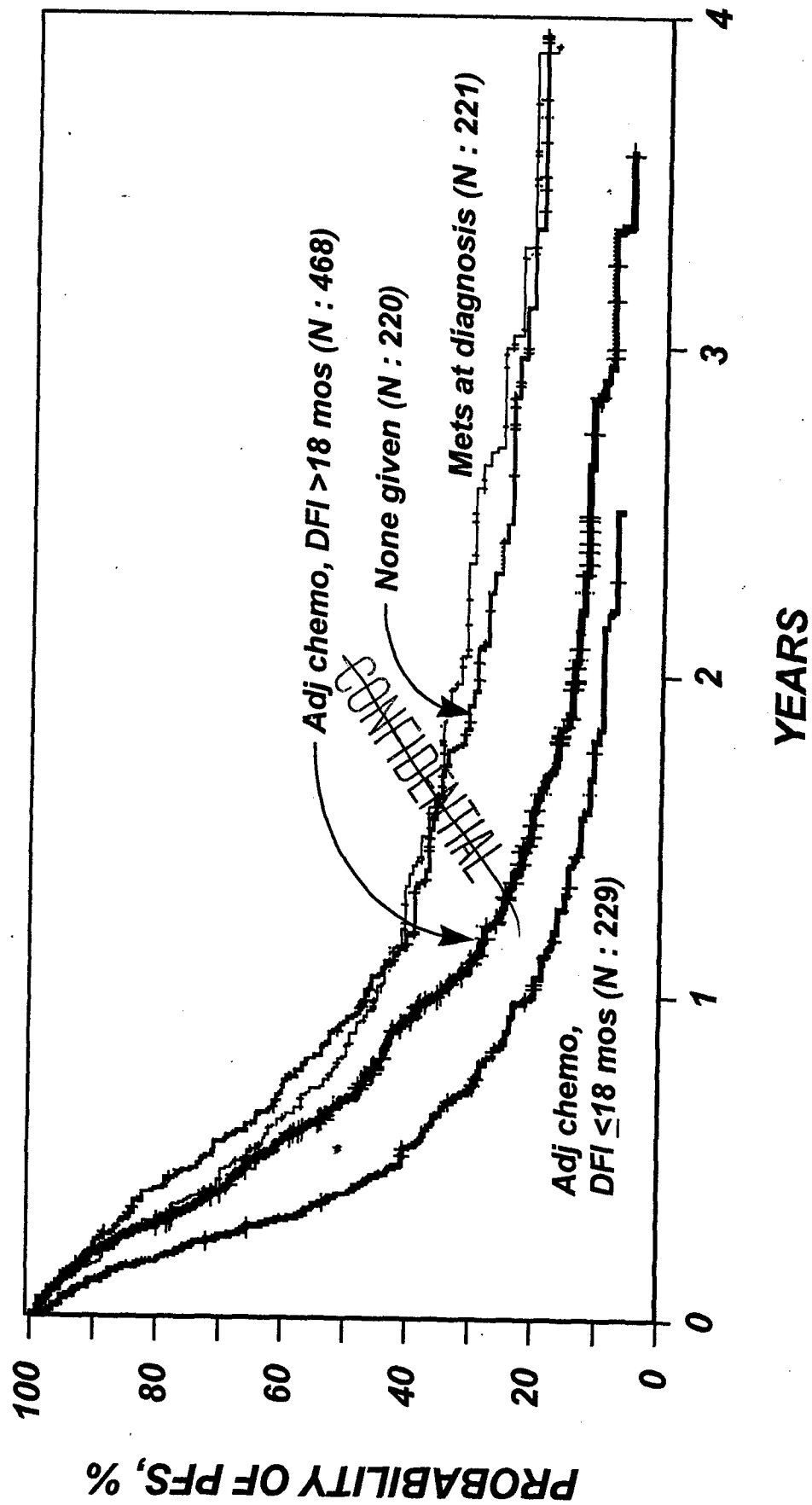
Appendix 4.13

BRS: Systemic
Berry, Donald

1999 Annual Meeting of the American Society of Clinical Oncology

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Abstract Categories: BRS. Systemic

Format Preference: Slide or Poster presentation Awards:

Audio/Visual: Yes
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CONVENTIONAL- VS HIGH-DOSE THERAPY FOR METASTATIC BREAST CANCER: COMPARISON OF CANCER AND LEUKEMIA GROUP B (CALGB) AND BLOOD AND MARROW TRANSPLANT REGISTRY (ABMTR) PATIENTS. D A Berry[1], G Broadwater[2], M C Perry[2], J Aisner[2], M Costanza[2], H Parnes[2], I C Henderson[2], L Norton[2], K Antman[3,4], J P Klein[4] and M M Horowitz[4]. [1]Institute of Statistics and Decision Sciences, Duke University, Durham, NC; [2]Cancer and Leukemia Group B (CALGB), Chicago, IL; [3]Columbia University, New York, NY and [4]Blood and Marrow Transplant (ABMTR) Registry, Milwaukee, WI.

We compared survival of women with metastatic breast cancer registered on 4 CALGB conventional-dose chemotherapy trials versus women registered with the ABMTR. The initial data set included 1621 CALGB patients treated in 1980-92 and 1188 ABMTR patients treated in 1989-95. CALGB protocols were: CALGB 8081 (cyclophosphamide[Cy], doxorubicin, and fluorouracil [CAF] vs Tamoxifen +CAF,n=458), CALGB 8281 (CAF vs vinblastine, doxorubicin, thiotepa[T], and halotestin [VATH] followed by Cy, methotrexate, fluorouracil, vincristine, and prednisone [CMFVP] at failure vs VATH alternating with CMFVP, n=484), CALGB 8642 (CAF vs phase II agent followed by CAF, n=452), CALGB 9140 (CAF vs CAF+ Leucovorin, n=227); there were no significant differences in outcomes between study arms or trials. 51% of ABMTR cases received high-dose CyT ± other drugs; various other regimens were used. Survival did not differ across regimens. We excluded 196 women with missing prognostic factor data. To minimize selection biases we focused on women with chemotherapy-sensitive disease and not more than 60 y of age. The study sample included 1217 women: 657 from CALGB, 560 from ABMTR. To minimize time to treatment bias, we used left-truncation; to adjust for potentially confounding prognostic factor differences we used Cox regression. A left-truncated univariate model showed significant survival benefit for autotransplant (relative risk of death [RR] 0.86, p=0.011); however, a multivariate model including disease-free interval after primary treatment, performance score, number of metastases and ER status showed no significant difference with high- vs conventional-dose therapy (RR=0.91, p=0.19). We conclude that some of the encouraging results of high-dose therapy in breast cancer may be due to patient selection and that careful controlled comparisons in large groups of women are needed to evaluate relative efficacy of these approaches.

Table 2: Patient, disease and transplant characteristics of 689 high-risk primary breast cancer patients (excludes stage III inflammatory) reported to the ABMTR from 1989 to 1996 by 70 teams worldwide.

Variable	N (%)
Number of Patients, N evaluable	689
Stage, N evaluable	689
Stage II	387 (56%)
Stage III	302 (44%)
Number of Reporting Centers	70
Year of Transplant, N evaluable	689
1989-1990	15 (2%)
1991-1992	156 (22%)
1993-1994	288 (42%)
1995-1996	230 (33%)
Age at Transplant, N evaluable	680
Median (range), years	44 (24-65)
Performance score pretransplant, N evaluable	668
< 90	46 (7%)
90-100	622 (93%)
Pathological Tumor Size, in cm, N evaluable*	486
Median (range)	3.5 (<1-16)
≤ 2	135 (28%)
2 to 5	234 (48%)
> 5	117 (24%)
Number of Positive Axillary Nodes, N evaluable*	556
Median (range)	12 (0-46)
≤ 9	171 (31%)
> 9	385 (69%)

* Excludes 86 patients receiving neoadjuvant chemotherapy

Variable	N (%)
Estrogen receptor status, N evaluable	661
Negative	231 (35%)
Borderline	22 (3%)
Positive	394 (60%)
None performed	14 (2%)
Adjuvant Therapy, N evaluable	658
CAF/FAC	443 (67%)
Other Anthracycline Regimens	151 (23%)
Other	64 (10%)
Surgery pretransplant, N evaluable	649
Mastectomy	558 (86%)
Lumpectomy	91 (14%)
Chemotherapy for initial management, N evaluable	676
Adjuvant	590
Stage II	362 (61%)
Stage III	228 (39%)
Neoadjuvant	86
Stage II	21 (24%)
Stage III	65 (76%)
Pretransplant hormonal therapy, N evaluable	650
Total receiving	75 (12%)
Estrogen Receptor positive	57/394 (14%)
Estrogen Receptor negative	11/231 (5%)
Estrogen Receptor borderline/not tested	3/22 (14%)

Variable	N (%)
Radiation Treatment, N evaluable	681
Pretransplant	90 (13%)
Post transplant	392 (58%)
Pre and post transplant	11 (2%)
None	188 (28%)
Conditioning Regimen, N evaluable	688
CBP	57 (8%)
CT	277 (40%)
CTCb	140 (20%)
CTM	26 (4%)
ICbE	46 (7%)
Other	142 (21%)
Source of Graft, N evaluable	689
Bone Marrow	234 (34%)
PBSC	291 (42%)
Bone Marrow + PBSC	164 (24%)
Interval from Diagnosis to Transplant, N evaluable	685
Median (Range)	7 (1-18)
Treatment to enhance PBSC collection, N evaluable**	436
Growth Factor Only	291 (67%)
Growth Factor and Chemotherapy	140 (32%)
Growth Factor in First 7 Days, N evaluable	665
None	51 (8%)
G-CSF	417 (63%)
GM-CSF	116 (17%)
G- and GM-CSF	81 (12%)

**Excludes 231 patients receiving bone marrow alone.

Variable	N (%)
Tamoxifen Treatment Post Transplant, N evaluable	680
Total Receiving	394 (58%)
Estrogen receptor positive	229/394 (58%)
Estrogen receptor negative	27/231 (12%)
Estrogen receptor borderline/not tested	9/22 (40%)

PBSC = peripheral blood stem cells, C = cyclophosphamide, B = BCNU, P=cisplatin, T = thiotepa, Cb = carboplatin, M=mitoxantrone, I = ifosfamide, E = etpopside

Table 3. Univariate analysis of survival and progressive-free survival (95% confidence interval) after autotransplant for high-risk primary breast cancer (excluding inflammatory) between 1989 and 1996.

Variable	N(%)	3yr Survival	P*	3yr DFS	P*	3yr TRM	P*
All Patients	689	72 (67-76)%	-	60 (56-64)%	-	5 (3- 7)%	-
Disease status	689		0.94		0.72		0.79
Stage II	387 (56%)	72 (66-78)%		61 (55-67)%		4 (2-6)%	
Stage III	302 (44%)	72 (65-78)%		59 (52-66)%		6 (3-10)%	
Age at dx	680		0.85		0.18		0.02
≤ 45	389 (57%)	72 (66-77)%		63 (57-68)%		3 (1-5)%	
> 45	291 (43%)	73 (66-79)%		57 (49-64)%		8 (4-13)%	
Year of transplant	689		0.06		0.47		0.08
1989-1991	60 (9%)	62 (49-74)%		53 (40-66)%		0	
1992-1996	629 (91%)	73 (68-78)%		61 (56-66)%		5 (3,8)%	
Performance score	668		0.15		0.048		0.66
<90	46 (7%)	66 (48-82)%		51 (32-70)%		6 (0-22)%	
≥ 90	622 (93%)	72 (68-77)%		61 (56-66)%		5 (3-8)%	
Tumor size	496		0.35		0.34		0.06
≤ 2	138 (28%)	67 (57-76)%		57 (47-67)%		10 (4-17)%	
2 to 5	236 (48%)	76 (69-82)%		64 (57-72)%		3 (1-6)%	
> 5	122 (25%)	75 (65-83)%		65(54-75)%		4 (1-9)%	
Number of positive axillary nodes	568		0.07		0.15		0.24
≤ 9	173 (31%)	67 (57-75)%		59 (50-68)%		8 (3-15)%	
> 9	395 (69%)	76 (70-81)%		63 (57-69)%		4 (2-7)%	
ER status pretx	625		0.0001		0.0001		0.23
Negative	231 (37%)	61 (53-69)%		48 (40-56)%		7 (3-12)%	
Positive	394 (63%)	79 (74-83)%		67 (61-73)%		4 (2-7)%	
Surgery pretx	649		0.87		0.87		0.09
Mastectomy	558 (86%)	72 (67-76)%		61 (56-66)%		4 (2-7)%	
Lumpectomy	91 (14%)	71 (59-82)%		61 (48-73)%		10 (4-20)%	
Radiation therapy	681		0.0001		0.0001		0.03
Pretx	90 (13%)	69 (57-79)%		54 (42-66)%		8 (2-16)%	
Posttx	403 (59%)	80 (76-84)%		67 (62-73)%		3 (1-6)%	
None	188 (28%)	56 (47-66)%		46 (37-55)%		7 (3-14)%	
Adjuvant Therapy	677		0.0001		0.0001		0.59
CAF/FAC	443 (65%)	74 (69-79)%		63 (58-69)%		4 (2-6)%	
Other Anthracyline	172 (25%)	71 (62-80)%		57 (47-66)%		8 (3-15)%	
Other	62 (10%)	66 (50-80)%		51 (35-66)%		3 (3-9)%	
Graft Type	689		0.66		0.67		0.7
BM	234 (34%)	71 (64-77)%		61 (54-68)%		6 (3-10)%	
PBSC	291 (42%)	73 (65-80)%		61 (52-69)%		3 (1-7)%	
BM+PBSC	164 (24%)	72 (64-80)%		60 (51-68)%		5 (2-9)%	

Variable	N(%)	3yr Survival	3yr DFS	P*	3yr TRM	P*
Mobilization	418			0.08		0.64		0.1
GF only	272 (65%)	67 (60-74)%	60 (52-67)%		5 (3-9)%	
GF and Chemo	146 (35%)	84 (75-91)%	59 (48-70)%		2 (0-6)%	
Conditioning Regimen	687			0.09		0.04		0.88
CBP	57 (8%)	74 (61-85)%	69 (60-82)%		4 (0-12)%	
CT	277 (40%)	75 (69-81)%	63 (56-70)%		5 (2-9)%	
CTCb	140 (20%)	73 (61-83)%	55 (43-67)%		5 (1-13)%	
CTM	26 (4%)	85 (69-96)%	81 (64-93)%		4 (0-16)%	
ICE	46 (7%)	72 (57-84)%	57 (42-72)%		4 (0-12)%	
Other	141 (21%)	58 (47-69)%	48 (38-59)%		5 (2-11)%	
GF in first 7 days	662			0.31		0.34		0.28
None	51 (8%)	66 (48-83)%	51 (34-68)%		0	
G	417 (63%)	74 (69-80)%	63 (57-69)%		6 (3-10)%	
GM	116 (18%)	77 (66-85)%	56 (45-66)%		2 (0-7)%	
G and GM	78 (12%)	64 (52-75)%	61 (49-72)%		7 (2-16)%	
Interval dx to tx	685			0.0001		0.0001		0.003
≤ 9 months	539 (79%)	75 (71-80)%	65 (60-70)%		4 (2-6)%	
> 9 months	146 (21%)	58 (47-68)%	43 (33-53)%		11 (5-20)%	

*P-value computed using the log-rank test.

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Table 4: Variables tested in multivariate analysis

Stage at transplant (stage II, stage III)
Age at transplant (<45, ≥45)
Year of transplant (1989-1991, 1992-1996)
Performance score pretransplant (10 to 80, ≥ 90)
Pathological tumor size (≤ 2 cm, >2 and ≤ 5 cm, >5 cm)
Number of positive axillary nodes (≤9, >9)
Estrogen receptor status/tamoxifen posttransplant (ER positive with tamoxifen, ER positive
     without tamoxifen, ER negative with or without tamoxifen)
Surgery pretransplant (mastectomy, lumpectomy, missing)
Neoadjuvant treatment (yes, no)
Hormone treatment pretransplant (yes, no)
Radiation treatment (none, radiation pretransplant, radiation posttransplant)
Adjuvant therapy (FAC, other anthrocycline, other)
Conditioning Regimen (CBP, CT, CTCb, CTM, ICE, other)
Months from diagnosis to transplant (≤9, >9)
Graft type (bone marrow, peripheral blood, bone marrow and peripheral blood)
Growth factors - started up to 7 days post transplant (None, G only, GM only, G and GM)
Treatment to enhance PBSC collection (growth factors only, growth factors and chemo)

Table 5: Multivariate analysis of survival for recipients of autologous transplants for high risk primary breast cancer (excludes stage III inflammatory) reported to the ABMTR by 70 centers worldwide.

Covariate	N (%)	RR	95% CI	P value
Estrogen Receptor Status/Tamoxifen Posttransplant	669			0.0001
ER negative with or without tamoxifen posttransplant	222 (32%)	1.00	---	---
ER positive with tamoxifen posttransplant	227 (34%)	0.42	(0.27,0.63)	0.0001
ER positive without tamoxifen posttransplant	159 (24%)	0.72	(0.48,1.07)	0.11
ER unknown with/without tamoxifen posttransplant	61 (10%)	1.15	(0.67, 1.98)	0.60
Radiation Treatment	669			0.0005
None	183 (27%)	1.00	---	---
Pretransplant	88 (13%)	0.65	(0.40,1.04)	0.08
Posttransplant				
First 7 months	92 (14%)	0.14	(0.005, 0.37)	0.0001
>7 months posttransplant	306 (46%)	0.80	(0.53, 1.21)	0.20
Time From Diagnosis to Transplant	669			0.005
> 9 months	145 (22%)	1.00	---	---
≤ 9 months	524 (78%)	0.57	(0.38,0.84)	0.005

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AUTOTRANSPLANTS IN MEN WITH BREAST CANCER

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The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

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Running Head: Autotransplants for male breast cancer

ABSTRACT

<u>Purpose</u>: To determine the outcome of high-dose therapy with autologous hematopoietic stem cell support (autotransplants) in men with breast cancer.

<u>Patients and Methods</u>: We studied 13 men receiving autotransplants for breast cancer and reported to the Autologous Blood & Marrow Transplant Registry (ABMTR) by 10 centers. Six men had Stage 2 breast cancer, four had Stage 3, and three had metastatic breast cancer. Of twelve tumors tested, all were estrogen receptor positive. Median age at transplant was 50 years. The most common conditioning regimen was cyclophosphamide, thiotepa and carboplatin (n=5); the remaining eight men received other alkylator-based regimens. Three men received bone marrow, eight received blood stem cells, and two received both for hematopoietic support.

<u>Results</u>: All patients had hematopoietic recovery. There were no unexpected regimen-related toxicities. Of ten men receiving autotransplants as adjuvant therapy, three relapsed three, five and 50 months posttransplant and died 16, 19 and 67 months posttransplant. Seven of ten are disease-free with median follow-up of 23 months (range, 6-50 months). Of three men treated for metastatic breast cancer, one had progressive disease and two recurrent disease at six, seven and 16 months posttransplant.

<u>Conclusions</u>: Results of autotransplants for male breast cancer appear similar to those reported for women receiving autotransplants for breast cancer.

INTRODUCTION

Male breast cancer accounts for fewer than 1% of all breast cancers. The annual incidence is <1 per 100,000 males (1,2). Stage at diagnosis is generally more advanced than in women, poosibly a result of delays in diagnosis. Anatomic factors may also contribute (3). The median age of men with breast cancer is five to ten years older than women with breast cancer (1-7). While, 64% of premenopausal and 75% of post-menopausal women have estrogen receptor (ER) positive cancers and 58% and 53%, respectively, have progesterone receptor (PR) positive tumors, according to a large study by Clark and colleagues (8), 80-90% of men have ER and PR positive breast cancer (1-7). Recent advances in the molecular biology of breast cancer have allowed detection of differences in the BRCA1 and BRCA2 mutations in hereditary and spontaneously occurring female and male breast cancers (reviewed in 9,10).

The standard therapy of breast cancer in men is similar to treatment in women, including surgery, radiation, hormone therapy and chemotherapy (1-7). Some investigators report outcomes in men to be the same as in women, when patients are matched for histopathology, receptor state and disease stage (3-6). Others suggest that men have poorer outcomes than women despite lower histologic grade, high ER content and small size (6).

Increasing numbers of women now receive high-dose chemotherapy with autologous hematopoietic stem cell support (autotransplant) for both metastatic and high-risk Stage 2/3 breast cancer (11). We studied 13 men receiving high-dose chemotherapy with an autotransplant and reported to the Autologous Blood and Marrow Transplant Registry (ABMTR).

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METHODS

Thirteen men were identified among 3,254 autotransplants for breast cancer reported to the ABMTR between January, 1989 and January, 1996 by 107 centers. Detailed patient-, disease-, treatment- and outcome-related data were obtained on standard ABMTR Report Forms.

The ABMTR is a voluntary working group of more than 120 transplant centers primarily in North and South America that contribute detailed data on their autologous blood and bone marrow transplants to the Statistical Center at the Medical College of Wisconsin. Participants are required to report all consecutive autotransplants; compliance is monitored by on-site audits. The ABMTR database includes data on about 50% of the autotransplants done in North and South America since 1989. Patients are followed longitudinally. Computerized error checks, physician review of submitted data, and on-site audits of participating centers ensure data quality.

RESULTS

Thirteen subjects were treated at eleven centers. Table 1 lists features at diagnosis. Median age was 49 years (range, 32-60 years). Of twelve cancers tested, twelve were ER positive and ten were PR positive. Twelve men had a mastectomy. One received pre-surgery chemotherapy. Ten men received autotransplants as adjuvant treatment, six for Stage 2 disease (all with greater than ten positive ipsilateral axillary lymph nodes) and four for Stage 3 disease (one with inflammatory breast cancer). All had received prior standard-dose adjuvant chemotherapy with an anthracycline-containing regimen. Three men had autotransplants for metastatic disease. One presented with Stage 4 disease; two developed metastases after presenting with Stage 1 and Stage 2 disease. All three men with metastatic disease had received

chemotherapy treatment for their metastases with an anthracycline-containing regimen. One had

a complete response, one a partial response and one stable disease prior to autotransplant.

Twelve of 13 men had Karnofsky performance scores of 90% or 100% at the time of

autotransplant. One patient with metastatic disease had a Karnofsky score of 80%. The one

patient receiving two autotransplants had a Karnofsky score of 70% prior to the second

transplant. Median interval from diagnosis to autotransplant was six months (range, 4-9 months)

for men with stage 2 or 3 disease and 12, 31, and 32 months for the three with metastatic disease.

Table 1 also lists types of graft, mobilizing agents, and high-dose therapy regimens. One

patient (#13) received a planned second autotransplant. Mobilized peripheral blood (n=9), bone

marrow (n=3) or both (n=2) were used for hematopoietic stem cell support. Five peripheral

blood collections were mobilized with hematopoietic growth factors alone and six with growth

factors and chemotherapy. High-dose therapy regimens consisted primarily of alkylating drugs.

The most common regimen was cyclophosphamide, thiotepa and carboplatin (n=5). Twelve of

13 men received hematopoietic growth factors after graft infusion. Nine of the ten men with

Stage 2 or 3 disease received primary chest wall radiation, two before, and seven after

autotransplant. Six of ten received hormonal therapy (tamoxifen) after autotransplant. One of

the men with metastatic disease received local radiation therapy to the chest wall after

autotransplant.

Median day to absolute neutrophil count >1.0 x 10^9/L was 12 days (range, 8-22 days).

Median day to platelet count >25 x 10^9/L was 14 days (range, 6-20 days). In three

autotransplants, the exact day of achieving absolute neutrophil count >1.0 cells x 10^9/L was not

reported and in four, the day to platelet count >25 x 10^9/L was not available. However, all

patients had evidence of hematopoietic recovery and became transfusion-independent. No

patient developed myelodysplasia or other bone marrow disorder. No grade 4 (World Health Organization) non-hematologic toxicities were reported.

Table 2 lists patient outcomes. Seven of ten men receiving autotransplants as adjuvant therapy are disease-free with median follow-up of 23 months (range, 6-50 months). Three men relapsed at three, five and 50 months posttransplant and subsequently died 16, 19 and 67 months posttransplant. All three men treated for metastatic breast cancer had evidence of progressive or recurrent disease after autotransplant. The patient who achieved a complete response to standard-dose chemotherapy received two autotransplants and relapsed five months after his second autotransplant. The patient transplanted after a partial response to standard-dose chemotherapy failed to achieve a complete response and progressed seven months posttransplant. The patient transplanted with stable disease achieved a complete response after autotransplant but relapsed 16 months later. Two subsequently died 12 and 23 months posttransplant. One is alive with progressive breast cancer 27 months posttransplant.

DISCUSSION

This ABMTR report is the only study of men receiving autotransplants for breast cancer. The treatment was well tolerated with no regimen-related deaths and no unexpected non-hematologic toxicities. The toxicity appears equivalent to previously published reports in women receiving autotransplants for breast cancer (11-14).

Although the number of subjects is small, the efficacy of autotransplant in these 13 men with high-risk breast cancer appear similar to results reported in women (11,12). Outcomes of the patients with metastatic disease were disappointing, however only three patients were available for analysis. Seven of 10 men receiving autotransplants as adjuvant therapy are alive

and disease-free. These results are encouraging when compared to historic results of treatment with standard chemo-, radiation and hormonal therapy for patients with locally-advanced disease (1-7). However, evaluation of more cases and longer follow-up will be necessary to determine the incidence of late recurrence and possibility for cure in this population. The relative efficacy of standard and high-dose chemotherapy in men with breast cancer is probably not evaluable given the rarity of this disease. However, these data suggest that indications for high-dose therapy developed in the ongoing randomized studies in women will be applicable to men. Additionally, it seems reasonable to recommend inclusion of men in randomized studies that examine the role of autotransplant for breast cancer.

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Patient Number	Age at Diagnosis	Disease Stage at Diagnosis	ER/PR Status	Number Positive LNs[3]	Reason for Transplant	Mobilizing Agents	Stem Cell Source	Conditioning Regimen	Posttransplant HGF
1	49	2	+/+	15/33	Adj	C,G	B	CyTCb	G
2	51	3, Inf	+/+	2/14	Adj	G	B	CyTCb	G
3	48	2	+/+	19/23	Adj	G	B	CyTCb	G
4	50	2	+/+	17/24	Adj	None	BM	CyT	G
5	43	2[2]	NT/NT	11/17	Adj	C,G	B	TCb	GM
6	53	2	+/-	21/28	Adj	C,G	B	TaCbT	G/Epo
7	48	2	+/+	13/20	Adj	C,G	Both	CyBP	G
8	60	3	+/+	9/15	Adj	G	Both	CyTCb	G
9	48	3	+/+	3/22	Adj	C,G,GM	B	CyCb	None
10	53	3	+/+	14/16	Adj	None	BM	ACyE	None
11[1]	37	4	+/+	Not done	Met	None	BM	CyEI	GM
12	49	1	+/+	0/6	Met	G	B	CyTCb	G
13	32	2	+/+	1/17	Met	C,G	B	MelT	G

Abbreviations: Inf = inflammatory; ER = estrogen receptor; PR = progesterone receptor; NT=not tested; LNs = lymph nodes; Adj = adjuvant; Met = metastatic; C = chemotherapy; G = granuolocyte colony stimulating factor; GM = granulocyte macrophage colony stimulating factor; B = blood; BM = bone marrow; Cy = cyclophosphamide; T = thiotepa; Cb = carboplatin; Ta = taxol; B = carmustine; P = cisplatinum; A = adriamycin; E = etoposide; I = ifosfamide; Mel = melphalan; HGF = hematopoietic growth factor; Epo = erythropoietin.

[1] All patients had mastectomies except for this patient who had an excision.

[2] Probably stage 2; tumor size not available.

[3] Lymph nodes at ipsilateral axillary dissection.

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Table 2. Patient outcome.

Patient Number	DFI, mos	Relapse	Survival, mos	Alive
1	48	No	48	Yes
2	20	No	20	Yes
3	18	No	18	Yes
4	3	Yes	16	No
5	32	No	32	Yes
6	5	Yes	19	No
7	37	No	37	Yes
8	28	No	28	Yes
9	18	No	18	Yes
10	50	Yes	67	No
11	16	Yes	23	No
12	NA	Yes	12	No
13	6	Yes	27	Yes

Abbreviations: DFI = disease-free interval; NA = not applicable.

period, one sample has been used for a child with thalassemia who now has no evidence of thalassemia. Since all children with sickle cell anemia and thalassemia are diagnosed at birth, TX can be considered before patients become CMV positive, iron overloaded or alloimmunized. The availability of our national resource offers standardized procedures for collection, transportation, storage and testing of UCB units as well as a resource to evaluate the role of UCB TX for patients with hemoglobinopathies. The absence of CMV, the ability to consider a TX without a complete HLA match in a young child, and the successful results of TX using UCB provide strong support for the recommendation that UCB be collected and cryopreserved in all families who have a child with a hemoglobinopathy. A national resource will provide an effective means to accomplish this goal and to collect information regarding efficacy of UCB-TX for patients with hemoglobinopathies. We conclude from our preliminary results that collection of UCB be encouraged in families that have a child with sickle cell anemia or thalassemia.

Abstract# 550   **Poster Board#/Session: 550-I**

TRANSPLANTABILITY AND THERAPEUTIC EFFECTS OF BONE MARROW-DERIVED MESENCHYMAL CELLS IN CHILDREN WITH OSTEOGENESIS IMPERFECTA. E.M. Horwitz, D.J. Prockop*, W.W. Koo*, L.A. Fitzpatrick*, P. Gordon*, M. Neel*, R. Pyeritz*, P. Orchard, M.K. Brenner. *St. Jude Children's Research Hospital, Allegheny University of the Health Sciences, Wayne State University, Mayo Clinic, and University of Minnesota. Memphis, Philadelphia, Detroit, Rochester, Pittsburgh, and Minneapolis, USA.*

Bone marrow stromal cells are mesenchymal progenitor cells that have been shown to differentiate to bone and muscle in vitro and in vivo in murine model systems. In principle, transplantation of these marrow derived mesenchymal progenitor cells would attenuate or possibly correct genetic disorders of bone, muscle, and cartilage in humans, however, clinical data to support this concept is lacking. We present data demonstrating marrow derived mesenchymal cell engraftment in humans and correlate this with clinical benefit. This report describes the results of allogeneic bone marrow transplantation in three children with severe osteogenesis imperfecta, a genetic disorder in which osteoblasts produce defective type I collagen, leading to osteopenia, multiple fractures, severe bony deformities and markedly shortened stature. Donor osteoblast engraftment was documented in cortical bone by biopsy at 1.5-2.0%, even though donor mesenchymal cells remained absent in the adherent fraction of recipient marrow aspirate. Three months later, representative specimens of trabecular bone showed histologic changes indicative of new dense bone formation. All patients had increased total body bone mineral content ranging from 21 to 29 grams (median, 28 grams) as compared with predicted values of 0 to 4 grams (median, 0 grams) for healthy children with similar weights. These improvements were associated with marked increases in growth velocity, up to the median for normal children in two cases and significantly reduced frequencies of bone fracture, up to 80% reduction. Our results demonstrate that marrow derived mesenchymal cells are transplantable and engraft in the osteogenic environment and confirm that these cells do not contribute to the recipient hematopoietic microenvironment. We conclude that allogeneic bone marrow transplantation can lead to engraftment of functional mesenchymal progenitor cells indicating the feasibility of this approach in the treatment of osteogenesis imperfecta and perhaps other mesenchymal stem cell disorders.

Abstract# 551   **Poster Board#/Session: 551-I**

ANALYSIS OF SHORT-TERM COSTS OF ALLOGENEIC TRANS-PLANTATION: RESULTS FROM THE INTERNATIONAL BLOOD AND MARROW TRANSPLANT REGISTRY/NORTHWESTERN UNIVERSITY ECONOMIC DATA BASE PROJECT. C.L. Bennett, T.M. Waters*, T.J. Stinson*, O. Almagor*, K.A. Sobocinski*, J.P. Klein*, P.A. Rowlings, M. Horowitz. *Northwestern University and VA Chicago Health Care System, Chicago IL; ABMTR/IBMTR, Medical College of Wisconsin, Milwaukee WI, USA.*

Allogeneic peripheral blood stem cell transplantation is an emerging technology, accounting for 22% of the 1997 allotransplants reported to the IBMTR. This study compared costs for patients with hematologic malignancies who received high dose therapy with standard allogeneic bone marrow (alloBMT) versus the new technology, allogeneic peripheral blood stem cell transplantation (alloPBSCT). Utilization and cost data were obtained for 72 patients with acute leukemia, 70 patients with CML, and 26 patients with non-Hodgkin's lymphomas who received care at 4 transplant centers in the U.S., from the time of mobilization through 100 days post transplant (exclusive of the costs of donor searches). Corresponding clinical data were obtained from the IBMTR. Hospital charges were converted to costs using department-specific cost to charge ratios and clinical data were merged with cost data. Median total costs were evaluated by disease and transplant source. For patients undergoing HLA-matched sibling alloPBSCT, median 100-day cost savings associated with the use of peripheral stem cells in comparison to bone marrow were 60% for AML/ALL ($62,654 versus $140,850, p < 0.01), and 30% for CML ($70,678 versus $98,853, p < 0.01), or NHL ($69,379 versus $106,420, p < 0.05). From 33% to 40% of the total transplant costs were for inpatient room care for patients with leukemia. Room costs accounted for 33% of the total costs for alloPBSCT NHL patients, and 22% of the total costs for alloBMT NHL patients. Pharmaceuticals were also costly, accounting for 25% to 33% of the total transplant costs for patients with AML/ALL. For NHL, pharmaceuticals were the single largest expenditure,

accounting for 40% of the total costs for alloBMT and >50% for alloPBSCT. Laboratory and blood bank costs each accounted for 6% to 14% of the total costs for leukemia and lymphoma patients. This study from four large transplant centers provides preliminary evidence of 30% to 60% cost savings in the first 100 days with alloPSCT. Longer term cost assessments are needed, particularly related to chronic graft versus host disease.

Abstract   **Session: 552-I**
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Appendix 4.16

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The _____ transplants makes the procedure applicable in older adults with hematologic malignancies and as an experimental treatment to induce graft-versus-tumor effects in cancer patients. Between 11/97-8/98 we treated 11 patients with fludarabine 25 mg/m^2 × 5 days and cyclophosphamide 60 mg/kg × 2 days followed by PBSCT from a G-CSF stimulated HLA matched (n = 10), or one HLA-A locus mismatched sibling donor (n = 1). The mismatched patient received additional ATG. Median transplant dose was 8 × 10^6 CD34+ and 2.4 × 10^8 CD3+ cells/kg. Cyclosporine (CSA) was given until day 30 then tapered to induce a graft-versus-malignancy (GMV) effect. Severe mucositis and VOD did not occur. Hematologic nadirs were brief and recovery was rapid, with a median time to platelets ≥20,000 of 6 days (range 0-15) and neutrophils ≥500 of 11 days (range 9-15 days). Transfusion requirements were low (median: 1 red cell and 1 platelet transfusion/transplant). Median hospital stay post transplant was 13 days (range 10-23). At the time of neutrophil recovery, minisatellite chimerism analysis showed donor engraftment in all patients, 10 with mixed chimerism and one 100% donor in myeloid and lymphoid lineages. Of 9 patients evaluable after day 45, 8 progressed to complete donor chimerism, and one had delayed graft failure followed by autologous recovery. Overall risk of TRM was 9%. Four patients developed grade II-III acute GVHD responsive to steroids (one mismatched transplant and 3 following CSA withdrawal). No patient has so far developed chronic GVHD. Only 3 patients developed CMV antigenemia, which resolved with gancyclovir. Five patients over 55 years (median 60, range 56-68) had hematologic malignancies (2 CML, 2 MDS, 1 NHL). Three survive in complete remission and one shows regression of lymphoma. One patient in a second chronic phase of CML relapsed into blast crisis and died. Six patients (median age 44, range 23-50) had metastatic tumors and had failed conventional treatment. Two renal cell carcinoma patients with pulmonary metastases at transplant survive, one in complete remission (day 200), one with stable disease (day 135). Four patients had melanoma: one survives with progressive disease following graft rejection; one, with evidence of tumor regression, died from transplant-related causes and two died from progressive disease. These results show that non-myeloablative transplants are tolerated well and have a low risk of TRM and GVHD. Sufficient donor engraftment was achieved to confer a GVM effect.

Abstract# 553   **Poster Board#/Session: 553-I**

SECONDARY ALLOGENEIC STEM CELL TRANSPLANTATION (ALLO SCT) USING A NON-MYELOABLATIVE CONDITIONING REGIMEN FOR PATIENTS WITH HEMATOLOGICAL MALIGNANCIES. A. Nagler, R. Or, E. Naparstek, G. Varadi*, R. BenYosef*, S. Slavin. *BMT Depts., Hadassah, Jerusalem, Israel.*

Therapeutic options for patients (pts) with hematological malignancies following autologous (auto) or allogeneic (allo) SCT is rather limited. Secondary allogeneic transplantation is associated with a high incedence of transplant related mortality (TRM) and toxicity (TRT) due to the mega doses of chemoradiotherapy traditionally used in the conditioning regimens. Recently we reported that it is possible to achieve fast engraftment and elimination of malignant cells with minimal procedure related toxicity by using a non-myeloablative conditioning regimen (Flu/BU/ATG) prior to alloSCT. Based on our experience we decided to use the same strategy for pts with hematological malignancies following auto or allo SCT. Since 12/96 ten very high risk heavily treated pts with hematological malignancies (NHL-4, AML-3 (secondary-2), ALL-1, CML-1, HD-1) have undergone secondary alloSCT (sibling-8, unrelated-2; PBSC-8, BM-2) with non-myeloablative conditioning 29 (6-61) months following their first SCT (auto-8, allo-2). Eight were male and 2 female, of median age 37 (13-63) years. Engraftment was fast, with WBC > 1 × 10^9/L and ANC > 0.5 × 10^9/L on day 15 (11-30), plt > 25 × 10^9/L on day 21 (15-∞) and plt > 50 × 10^9/L on day 28 (19-∞) post alloSCT. TRT was minimal, with no VOD, renal or pulmonary toxicity. Only one pt (10%) with protracted resistant thrombocytopenia developed grade IV hemorrhagic cystitis and died. Two pts (20%) developed acute GVHD (Grade II) and other 3 (30%) chronic GVHD (moderate-2, mild-1). Two very high risk pts with NHL relapsed 2 and 9 months post alloSCT and died. Seven pts are alive with 100% donor chimerism and no evidence of disease, after a median follow-up of 7 (2-16) months. We suggest that non-myeloablative conditioning significantly reduces transplant related toxicity and thus makes secondary alloSCT feasible. Our preliminary results should be confirmed in a larger group of pts with a longer follow up.

Appendix 4.17

Safeguarding the administration of high-dose chemotherapy: a national practice survey by the American Society for Blood and Marrow Transplantation

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ABSTRACT

Overdoses of high-dose chemotherapy before hematopoietic cell transplantation are serious adverse events, but their frequency and etiology are unknown. The American Society for Blood and Marrow Transplantation (ASBMT) conducted an anonymous national survey to identify errors in safety practices during the administration of high-dose chemotherapy. The questionnaire was returned from 115 (68%) of 170 hematopoietic transplant centers in the United States. Ninety-four of the programs were university or affiliated centers, 19 were community hospitals, and 41 were founded since 1990. A total of 7650 transplants were reported for 1994: 22% of the programs performed 1–20 transplants, 60% performed 21–100 transplants, and 18% performed more than 100 transplants. Fifteen of the 115 responding centers reported a total of 18 patients inadvertently given overdoses of cisplatin (n=3), carboplatin (n=2), busulfan (n=2), cytosine arabinoside (n=2), cyclophosphamide (n=2), interleukin-2 (n=2), or other agents (n=5) between 1989 and 1994. Cumulative drug doses given as a daily dose (six cases) and nursing infusion errors (six cases) were the most common errors. The estimated chemotherapy overdose error rate was 0.06%, or 6 cases/10,000 transplants, with 95% confidence limits of 0.03–0.11%. The overdose rate among more experienced centers in operation before 1990 was lower than that among newer centers ($p < 0.01$). Large centers (>100 transplants performed in 1994) experienced errors at rates lower than those in medium-sized centers (21–100 transplants, $p = 0.03$). Although the number of events was small in this self-reporting survey, overdoses were noted in 13% of the responding centers, especially among more recently established units. Safety practices need to emphasize multidisciplinary checkpoints at the physician, pharmacist, nursing, and institutional levels. Based on these survey results, ASBMT recommendations for further safeguards for high-dose chemotherapy administration are proposed.

KEY WORDS

Bone marrow transplantation • High-dose chemotherapy • Medication errors • Physician orders

INTRODUCTION

High-dose chemotherapy followed by marrow or peripheral blood stem cell transplantation is widely used for the treatment of hematologic and malignant disorders [1–3]. Recent episodes of accidental overdose of myeloabla-

tive chemotherapy have been widely publicized and call into question the safety of these procedures [4–6]. The frequency and nature of overdoses are poorly understood, however, as are the implementation and reliability of practices designed to prevent their occurrence.

Medical practice errors take many forms. They include mistakes made by physicians, nurses, pharmacists, and ancillary personnel when ordering and administering treatments and medications, or performing procedures such as surgery or blood transfusion [7–10]. The Harvard Medical Practice Study found that in 1984 negligent care caused 28% of iatrogenic injuries, which afflicted 3.7% of all hospitalized patients in New York state [7]. Based on that study, it has been estimated that accidental injuries are likely to affect over a million hospitalized people each year in the United States [11]. The costs associated with such adverse events are substantial, further underscoring the need for investment in prevention [12]. Analysis of causal relationships has shown that many errors could be prevented through the implementation of well-designed regulations and policies; accordingly, several guidelines for preventing medication errors have been proposed as standards of care [13–20].

To enhance the safety of high-dose chemotherapy administration, the Executive and Practice Committees of the American Society for Blood and Marrow Transplantation (ASBMT) designed a questionnaire to evaluate chemotherapy practices in the United States from 1989 to 1994. Our hypothesis was that overdoses were associated with identifiable patterns of practice. The study was designed to meet the following objectives: 1) investigate the nature and frequency of overdose errors; 2) describe current safeguard systems in transplant centers; 3) determine whether the absence of certain safeguards was related to overdose errors; 4) determine whether center characteristics were related to errors or practice policy; and 5) describe planned policy and practice modifications.

METHODS
Transplant centers

Pediatric and adult blood and marrow transplant units in the United States were identified from the International Bone Marrow Transplant Registry (IBMTR) and the Autologous Blood and Marrow Transplant Registry-North American (ABMTR). The IBMTR has collected data from over 300 institutions performing allogeneic marrow transplants worldwide since 1972. In 1991, the ABMTR began collecting data on transplants using autologous marrow or blood stem cells performed in North America. These lists were further updated by members of the Executive and Clinical Practice Committees of ASBMT. A total of 176 centers were identified in 44 states. The eight states with the greatest number of transplant centers were California (24), New York (13), Texas (11), Illinois (11), Florida (9), Ohio (9), Pennsylvania (8), and Massachusetts (7).

Data collection and survey respondents

A self-reporting anonymous form surveyed center attributes, clinical practices, quality control measures for ordering and delivering chemotherapy, and circumstances and detection of prior overdose errors (Appendix). Areas

surveyed included: center characteristics, chemotherapy ordering practices, pharmacy policies, nursing practices, quality control and review, cause and detection of overdoses, and current safeguard systems and plans for modifications. The anonymous questionnaire was mailed to 176 program directors. Six were returned as incorrect center identification or no longer involved in transplantation. Replies were received from 115 (68%) of the 170 centers after a second survey was facsimiled to all centers.

To assess possible sampling biases among respondents, one of the authors (M.M.H.) compared the reported characteristics of the 115 anonymous centers with those of a larger sample of US centers using the IBMTR or ABMTR database for the same 5 year period. A total of 139 programs were included in the database for comparison. Seventy centers participating in one or both registries at some time over the past 7 years could not be included because of incomplete data for the years of the current survey. Many of these centers either began performing transplants or joined the registry recently.

Statistical analysis

Statistical comparisons of our samples with the IBMTR or ABMTR database sample were performed with Chi-square test or Fisher's exact test if any categories occurred very infrequently. Logistic regression was used to analyze the occurrence rate of overdose errors. Missing or ambiguous responses complicated some analyses. All 115 centers provided information on cases of chemotherapy errors, however, 17 centers failed to furnish data on the cumulative number of patients transplanted. Due to the anonymous nature of this survey, we were not able to recover omissions or clarify ambiguous data. We used Rubin's multiple imputation method for missing data in conjunction with the logistic regression approach so that cases with partial responses could be included [21,22]. Multiple imputation allows calculation of rate estimates, confidence intervals, and test statistics, which are adjusted for the fraction of missing information. Intermediate predictor variables used to generate the multiple imputation values for the 5-year transplant totals were current number of transplant-dedicated beds, number of transplants in 1994, and years of center operation.

We recognized that the time frame (Appendix, item 1e) requesting the cumulative number of transplanted patients could have been interpreted in several ways. All analyses involving error rates were repeated assuming each of three possible interpretations (i.e., a cumulative total of 4, 5, or 6 years). Rate estimates varied only slightly under the different assumptions (1/10,000). Rate estimates presented in the text are the median values computed under each set of assumptions, and confidence intervals represent the smallest intervals spanning all three computed intervals. P-values given for comparisons of error rates in relation to center characteristics are the maximums of the three found under each set of assumptions. All p-values presented are two-sided.

RESULTS
Transplant center characteristics

The majority (75%) of hematopoietic cell transplant programs are located in university hospitals or academic research centers (Table 1). A minority (17%) of centers

perform only pediatric transplants. Forty-eight (42%) centers conduct only adult and 46 (41%) centers perform both adult and pediatric transplants. Most programs perform both allogeneic and autologous grafts. One hundred eleven (97%) centers are members of national cancer cooperative groups (CALGB, Cancer and Leukemia Group B; SWOG, Southwest Oncology Group; ECOG, Eastern Cooperative Oncology Group; CCG, Children Cancer Groups; POG, Puget Sound Oncology Group) or transplant registries (IBMTR or ABMTR) or both. Sixty-nine (60%) centers, including ten community hospitals and 59 university or research centers, had an external peer review site visit within the preceding 3 years. The characteristics of survey respondents were compared with those of centers in the IBMTR or ABMTR databases. More centers reporting to IBMTR or ABMTR databases performed autologous transplants only (11 vs. 23%, $p = 0.01$) and used peripheral blood stem cells as the only graft source (2 vs. 9%; $p = 0.02$). Otherwise, center characteristics did not differ significantly between the two groups for type of center, age range of patient treated, membership status of cancer cooperative groups, and number of dedicated transplant beds (data not shown).

Among 114 respondents reporting the year the program began, the median inaugural year was 1988. Forty-one (36%) programs were started since 1990. Fourteen (12%) programs were founded before 1980, and 59 (52%) programs were founded between 1980 and 1989 (one not specified). For centers reporting data to IBMTR or ABMTR, 63 (47%) started operations since 1990, which suggests that new centers may be underrepresented in the ASBMT survey ($p = 0.08$).

In the survey group, a total 7650 hematopoietic cell transplants in 109 centers (six nonresponses) were performed in 1994, with the annual number of transplants per center ranging from 2–460 (median 45) (Table 2). Among the 109 reporting centers, 24 (22%) programs performed 1–20 transplants, 65 (60%) performed 21–100 transplants, and 20 (18%) performed more than 100 transplants in 1994. The transplant numbers were compared with those reported to the IBMTR or ABMTR. For the most recent year, the survey sample included fewer small centers and more large centers than the IBMTR/ABMTR sample ($p = 0.04$). Between 1989 and 1994, a total of 22,542 transplants were recorded at the 98 centers responding to this survey (range of 2–2586, median of 121). By considering the 1994 data with the 1989–1994 totals for centers with incomplete responses, however, we estimated that a minimum of 24,255 transplants occurred at the 115 participating centers.

Safety practices and quality control

As shown in Table 3, 98 (85%) centers used preprinted chemotherapy order sheets. Among the 98 centers, 12 used preprinted orders for some but not all conditioning chemotherapy. A total of 94 centers listed the chemotherapy dose per date in the preprinted orders and 74 centers included the dose per course in the preprinted orders. Reasons given for not using preprinted orders included: treatment off-protocol (seven centers), small accrual protocols (six centers), and new protocols (two centers). Chemotherapy orders were signed by physician's assistant, resident, fellow, and attend-

Table 1. *Characteristics of 115 transplant programs*

	Number (%)
Type of center (n=113)	
University hospital, affilliated hospital, or research center	85 (75%)
Community hospital, university affiliated	9 (8%)
Community hospital, non-university affiliated	19 (17%)
Type of transplant	
Graft source (n=115)	
Both blood and marrow	109 (95%)
Peripheral blood stem cell only	2 (2%)
Bone marrow only	4 (3%)
Donor (n=114)	
Autologous and allogeneic (no unrelated)	51 (45%)
Autologous, allogeneic, and unrelated	49 (43%)
Autologous only	13 (11%)
Allogeneic only	1 (1%)
Type of patients treated (n=113)	
Both adult and pediatric patients	46 (41%)
Adult patients only	48 (42%)
Pediatric patients only	19 (17%)
Member of cancer cooperative groups[a] or transplant registry (n=115)	
Cooperative groups, ABMTR, and IBMTR	66 (58%)
Cooperative groups and ABMTR	15 (13%)
Cooperative groups and IBMTR	7 (6%)
ABMTR and IBMTR	6 (5%)
Cooperative groups only	10 (9%)
ABMTR	6 (5%)
IBMTR	1 (1%)
None	4 (3%)
Number of dedicated transplant beds (n=112)	
1–5	30 (27%)
6–10	45 (40%)
11–20	23 (21%)
21–30	8 (7%)
31–60	6 (5%)
Peer review site visit within last 3 years (n=115)	
NIH	30[c]
FDA	10[c]
Cooperative groups	25[c]
Others[b]	17[c]
None	46 (40%)

[a]*Cooperative groups include Cancer and Leukemia Group B (CALGB), Southwest Oncology Group (SWOG), Eastern Cooperative Oncology Group (ECOG), Puget Sound Oncology Group (POG), and Children Cancer Groups (CCG).*
[b]*Other mechanisms include by State, National Surgical Adjuvant Breast and Bowel Projects (NASBP), National Marrow Donor Program (NMDP), American Association of Blood Banks (AABB), College of American Pathologists (CAP), American Society for Histocompatibility (ASHI), panel of experts or cancer center review. Eleven centers were reviewed by two or more groups.*
[c]*Some programs indicated more than one review mechanism; therefore, percentage is not given.*

ing in 22, 24, 57, and 107 centers, respectively. Among the eight centers where order sheets were not signed by attendings, four required no mandatory co-signatures.

The chemotherapy dose was recalculated in the pharmacy in 106 (92%) centers. Chemotherapy dose verification was performed by one pharmacist in 66, two pharmacists in 38, or three pharmacists in one center (one not specified). Six centers indicated no dose recalculation by a

Table 2. *Number of transplants in 1994 and 1989–1994*

| | 1994 | | | 1989–1994 | |
| | Center number (%) | | | Center number (%) | |
Transplants	ASBMT survey	IBMTR/ABMTR	Transplants	ASBMT survey	IBMTR/ABMTR
1–5	5 (5%)	10 (7%)	1–50	28 (29%)	39 (28%)
6–10	6 (6%)	19 (14%)	51–100	14 (14%)	27 (19%)
11–20	13 (12%)	30 (22%)	101–200	28 (29%)	30 (22%)
21–40	26 (24%)	27 (19%)	201–400	17 (17%)	29 (21%)
41–60	21 (19%)	21 (15%)	>401	11 (11%)	14 (10%)
61–100	18 (16%)	21 (15%)	Not specified	17	—
101–200	13 (12%)	8 (6%)	Total number of centers	115 (100%)	139 (100%)
>201	7 (6%)	3 (2%)			
Not specified	6	—			
Total number of centers	115 (100%)	139 (100%)			
	$p = 0.04$			$p = 0.65$	

pharmacist, but four of the six used computer programs for drug ordering. Sixty-nine (60%) centers operated a computer system for drug ordering and dose limits were set by computer in 22 of the 69 centers. All 115 centers indicated that the chemotherapy dose and drug in bag were identified by nursing staff. Nursing verification of chemotherapy infusions was carried out by two nurses in 66 (57%) centers and one nurse in 42 (37%) centers (seven [6%] not specified). Doses were verified against orders in 111 (97%) centers and against the protocol in 73 (64%) centers by nurses. Patient identification and dose verifica-

tion against orders were not performed in five and three centers, respectively.

Among the 98 centers using preprinted orders, 15 have one, 71 have two to four, and 11 centers have five to six quality control reviews of the order forms (one did not specify). Reviewers included primary investigators (76 centers), medical directors (69 centers), pharmacy directors (33 centers), nursing directors (24 centers), research nurses (43 centers), and others (23 centers). Multidisciplinary standard practice committees (72 centers [63%]) and transplant quality assurance committees (76 centers [66%])

Table 3. *Safety practices for high-dose chemotherapy administration in 115 centers*

	Routinely used (%)	Not used (%)	Not specified
Chemotherapy orders			
Preprinted chemotherapy orders used	98[a] (85%)	17 (15%)	0
Preprinted orders used for each drug[b]	84	12[a]	2
Dates of chemotherapy[b]	96	1	1
Dose per day[b]	94	3	1
Dose per course[b]	74	23	1
Protocol drug dose typed on the orders	93 (81%)	19 (17%)	3
Protocol number specified on the orders	74 (64%)	36 (31%)	5
Chemotherapy infusions			
Pharmacy verification			
Pharmacist recalculates dose	106 (92%)	6 (5%)	3
Dose verified against protocol	87[d] (76%)	23 (20%)	5
Computerized drug order	69[e] (60%)	45 (39%)	1
Program sets dose limit[c]	22[e] (32%)	43 (62%)	3
Nursing verification			
Dose and drug in bag verified	115 (100%)	0 (0%)	0
Dose verified against orders	111 (97%)	3 (2%)	1
Patient identification verified	109 (95%)	5 (4%)	1
Dose verified against protocol	73 (64%)	41 (35%)	1
Patient weight and body surface area verified	90 (78%)	23 (20%)	2

[a]*See Results section.*
[b]*Based on the 98 centers using preprinted orders.*
[c]*Based on the 69 centers using computerized drug orders.*
[d]*One program indicated that only some chemotherapy doses were verified against protocol.*
[e]*One program indicated that only some chemotherapy was computerized and had dose limits set.*

were common components of quality control. Other committee or group reviews included medical advisory and staff conferences, policy and procedures, critical care, infection control, and transfusion committees. Eighty-seven centers (78%) had all protocols reviewed by the Institutional Review Board (IRB). Twenty-five centers, including 18 university affiliated centers, six community hospitals, and one of unspecified type, indicated that not all stem cell transplant protocols were reviewed by the IRB. Exemptions included transplants considered as standard treatments (16 centers), non-research protocols (four centers), and other reasons (three centers).

Nature and frequency of overdose errors

Fifteen centers reported a total of 18 individuals who received overdoses of high-dose therapy between 1989 and 1994. Twelve centers reported one case each and three reported two cases. The center characteristics, circumstances surrounding the errors, methods of detection and subsequent policy revisions are detailed in Table 4. The overdosed agents included cisplatin (n=3), carboplatin (n=2), busulfan (n=2), cytosine arabinoside (n=2), cyclophosphamide (n=2), interleukin-2 (n=2), doxorubicin, adriamycin, vincristine, methotrexate, and the combination of thiotepa, carboplatin, and etoposide (one each).

Cumulative drug doses given as a daily dose (six cases) and nursing infusion errors (six cases) were the most common types of error, followed by ambiguous orders without attending co-signatures (two cases), new protocols without preprinted orders (two cases), and pharmacy or staff errors (one each). Three centers (cases 14, 15, and 17) using computer programs for dose limitations had errors in physician orders (two cases) or pharmacy verification (one case). The consequences of overdoses were provided for eight cases, including death (case 15), clinical toxicity (cases 2, 13, 14, 16, 17, and 18), and no toxicity (case 6).

Overdose errors prompted policy revisions at ten centers: using preprinted orders; verifying an order against protocol; ordering a list of maximum drug dose; limiting orders to daily dose; verifying all chemotherapy orders by attending physicians, pharmacists and nurses; and increasing education and training. In addition, seven centers (nine cases) described their revision as reinforcing multidisciplinary checkpoints. Of the programs that were not planning to change their policies, six centers (cases 6–12 and 16) reported that multiple safety checkpoints were in place before errors occurred.

The overall rate of chemotherapy overdoses for the 5-year period was 0.06%, or 6 cases in 10,000 transplants, with 95% confidence limits of 0.03–0.11%. Univariate regression analyses detected a lower error rate among large centers (>100 transplants in 1994) than among medium-sized centers (21–100 transplants) ($p = 0.03$); however, there was no evidence that small centers (1–20 transplants) differed from medium-sized programs ($p = 0.99$). Centers in operation before 1990 also had a statistically significant lower error rate ($p < 0.01$). These two findings are closely linked because the older centers are also generally larger. Results also suggest a trend that centers reporting verification by two nurses rather than one might have a lower error rate ($p = 0.11$). Other center characteristics that did not show a statistical association with error rates included

community hospital (university affiliated or non-affiliated) vs. university hospital/research center and the presence of computerized drug ordering ($p > 0.35$).

DISCUSSION

This study profiles transplant programs and safety practices for high-dose chemotherapy administration in the United States. Patients were treated in a variety of settings ranging from community hospitals to university research centers throughout the nation. In sampling this broad constituency for reporting overdose errors, we obtained a high proportion of responses. The 68% response rate to this anonymous survey was high given that only one blinded, follow-up reminder was sent to all program directors. This response rate was similar to or higher than return rates in many unblinded surveys [23–25].

Comparison with the IBMTR or ABMTR databases examined the potential for selection bias in the responding sample. Small or new centers may not have responded to this survey as readily as older or larger ones. The registry database consistently comprises about 50% of autotransplants and 40% allotransplants in the United States. Their representations were evaluated and confirmed independently [26; MMH, unpublished data, 1997]. Even though the transplant registries do not receive all the transplant reports, the total number of transplants in the United Stated can be estimated. About 50,000 transplants (18,000 allogeneic and 32,000 autologous) were performed between 1989 and 1994, and 10,000–12,000 transplants (3–4,000 allogeneic and 7–8,000 autologous) in 1994. Thus, the total number of transplants reported here for 1994 reflects a significant proportion (64–77%) of all hematopoietic cell transplants performed in the United States.

The reported overdose rate, 6 cases/10,000 transplants in a 5-year period, is lower than overall medication error rates reported in the Harvard Medical Practice Study [7]. In that retrospective study with a sample size of 30,195 hospitalized patients, the adverse event rate was 3.7% and drug complications were the most common type of adverse events (19% of the total), which could be translated into a rate of 70 cases/10,000 patients. It should be emphasized that a direct comparison of our results with this reported error rate is problematic. Our survey focused on high-dose chemotherapy overdose, which represents one of the most severe forms of adverse drug events, but did not address the issue of overall drug-related adverse events. It is possible that non-chemotherapy medication errors also occurred, but that information was not provided. Moreover, though the self-reporting survey is a method of error identification frequently used in the literature, errors are not reported unless discovered. Accordingly, self-reported error rates tend to be lower than the actual rates. Despite the limitations of this approach, the purpose of our survey was to provide an opportunity for self-examination of practices. In addition, it provided a method of collecting and analyzing data on chemotherapy errors in settings where treatments were often new and intensive with overdoses potentially resulting in serious consequences.

In this survey, the most common types of errors were cumulative drug doses given as the daily dose and nursing

Table 4. *High-dose chemotherapy overdose errors and policy changes*

Case	Program starting year	Center type[a]	Transplants in 1994	Type of errors[b]	Drug	Method of detection	Policy change	Reinforced safeguard systems
1	Before 1990	U	21–100	Cumulative dose given for daily dose (3-fold overdose)	Doxorubicin	Nurse recognized errors later	Yes	Pharmacy verify protocols
2	Since 1990	U	21–100	Cumulative dose given for daily dose (4-fold overdose)	Cisplatin	Review of chart/toxicity	Yes	Use preprinted orders; pharmacist verify doses; dedicated nurses on transplant
3	Since 1990	U	>100	Cumulative dose given for daily dose	Cisplatin	Pharmacy detected error later	Yes	Multidisciplinary checkpoints; list maximum drug doses for treatments
4	Since 1990	U	>100	Cumulative dose given for daily dose	Cisplatin	Pharmacy detected error later	Yes	Multidisciplinary checkpoints; list maximum drug doses for treatments
5	Before 1990	U	>100	Cumulative dose given for daily dose	Adriamycin	Pharmacy detected error later	Yes	Limit orders to daily dosing
6	Before 1990	U	>100	Cumulative dose given for daily dose, no attending co-signature (3-fold overdose)	Carboplatin	Pharmacy detected error later	No	Multidisciplinary checkpoints; new protocol orientation; attending co-signs orders
7	Since 1990	C-UA	21–100	Nursing error (b.i.d. dose given concurrently, 2-fold overdose)	Cytosine arabinoside	Physician monitoring	No	Multidisciplinary checkpoints
8	Since 1990	C-UA	21–100	Nursing error (b.i.d. dose given concurrently, 2-fold overdose)	Cytosine arabinoside	Physician monitoring	No	Multidisciplinary checkpoints
9	Before 1990	C	21–100	Nursing error (24-hour infusion given in 6 hours)	Cyclophosphamide	Nurse recognized errors later	No	Multidisciplinary checkpoints
10	Before 1990	U	21–100	Nursing error and pharmacy error	Busulfan	Nurse recognized errors later	No	Multidisciplinary checkpoints
11	Since 1990	C-UA	21–100	Nursing error	Interleukin-2	Pharmacy detected error later	No	Verify orders and doses against protocols by pharmacists
12	Since 1990	C-UA	21–100	Nursing error	Interleukin-2	Pharmacy detected error later	No	Verify orders and doses against protocols by pharmacists
13	Before 1990	U	21–100	Ambiguous orders and no attending co-signature	Carboplatin	Laboratory monitoring, increase creatinine	Yes	Review preprinted orders; attending co-signs orders
14	Since 1990	U	21–100	Ambiguous orders and no attending co-signature	Vincristine	Clinical toxicity	Yes	Attending co-signs orders
15	Before 1990	U	21–100	New protocol and no preprinted orders	Cyclophosphamide	Review of chart	Yes	Use preprinted orders; increase awareness
16	Before 1990	N	>100	New protocol and new fellow	Thiotepa/ carboplatin/ etoposide	Attending detected error	No	Multidisciplinary checkpoints
17	Before 1990	N	21–100	Pharmacy error	Methotrexate	Clinical toxicity	Yes	Multidisciplinary checkpoints; review chemotherapy policies
18	Before 1990	U	>100	Unable to check busulfan blood level	Busulfan	Clinical toxicity	Yes	Centralized incident reports; attending verify all orders

[a]U, *university hospital or research center; C-UA, university affiliated community hospital; C, community hospital; N, not specified.*
[b]*Details varied among centers; all descriptions included.*

infusion mistakes; however, overdoses occurred at every step between the processes of ordering and administering. Error rates were higher among newer centers established after 1990, which also tended to be smaller units, suggesting that centers with more experience in high-dose chemotherapy may be more likely to avoid errors. Alternatively, errors may have been recognized in the past and safeguards subsequently strengthened. We did not find individual safeguard measures that were statistically associated with reduced rates of error.

Center variation in marrow or blood stem cell transplantation outcome is more difficult to study, due in part to wide variations in treatment protocols and patient selection. While data from this survey showed that larger and more experienced centers have lower reported error rates, these findings should be interpreted with caution and should not be used as surrogate markers of hospital performance or outcome since variables associated with voluntary reporting make comparisons between institutions difficult [27].

Safety practices for chemotherapy administration were studied at the physician, pharmacist, and nursing levels. While all centers had procedures in place to prevent chemotherapy errors, the degree of thoroughness differed. Com-

puter programs for drug orders and dose limits may have prevented errors; however, this issue was not addressed by this survey. Importantly, some errors occurred even with computer monitoring in place. Dose verification against protocols as well as confirmation of the patient's weight and body surface area were less commonly performed. Twenty-four centers noted that residents wrote chemotherapy orders which were countersigned by either fellows or attendings.

Our findings are consistent with earlier reports that medication errors frequently occur as a result of multisystem failures. Adverse events and injuries are serious and costly complications of health care and represent a wide range of potential events or errors. Many adverse drug events analyzed in the Harvard study were complex in nature. Episodes were attributed to various problems of process or unique errors caused many categories of adverse drug events. With a systemic approach, errors can be reduced by examining elements and interrelationships of the safety structure [17,18,28,29]. The magnitude of iatrogenic events is probably underestimated since most studies have focused only on injury. Error rates have been distressingly high when errors were specifically audited. For example, autopsy studies indicated high rates (35–40%) of missed diagnosis causing death [30–32]. The annual national cost of such drug-related morbidity and mortality has been estimated at $76.6 billion, with the majority ($47 billion) related to hospital admissions associated with drug therapy [12]. Two recent reports have quantified the additional resource utilization associated with these events [33,34]. Data from the prevention study suggested the annual costs attributable to all adverse events and preventable events for a 700-bed teaching hospital were $5.6 million and $2.8 million, respectively.

Marrow and peripheral blood stem cell transplants are increasingly used to treat an array of diseases. This factor in turn has led to the establishment of a large number of centers since 1990. It is possible that some newer centers may have less established safeguard systems. More importantly, no standard practice guidelines have been previously formulated for transplantation. To reduce errors in conventional dose chemotherapy, several measures have been suggested, including certification examinations for oncology-trained pharmacists [19,20]. Despite policies in place in many centers, overdose errors did occur, which underscores the need for enhanced guidelines and diligent monitoring.

Based on the published literature and the findings of this survey, ASBMT proposes specific guidelines for high-dose chemotherapy (Table 5). These guidelines emphasize the need for a multidisciplinary approach to standardizing safety practice and apply to all transplant centers regardless of type, size, or experience of the program. Preprinted order sheets should specify the date and daily doses of a drug, which will prevent physicians from prescribing the cumulative drug treatment as the daily dose. Likewise, verifying patient and drug identification against orders and protocols by two nurses will reduce the incidence of nursing infusion errors. On an institutional level, periodic case review and monitoring safeguards and errors will assist in early identification of adverse events. Medication errors should be viewed as system failures that require prompt remedy. Thus, the reporting process should be simple and

Table 5. *ASBMT guidelines for high-dose chemotherapy administration*

Physician procedures
  Physician uses preprinted orders that specify protocol number and name of the study
  Preprinted orders specify the daily drug dose and specific dates for all chemotherapy
  Physician verifies that two staff members independently confirm patients' height and weight
  Attending physician verifies the name, protocol number, and recalculates the drug dose
  Attending physician co-signs all chemotherapy orders.
Pharmacist procedures
  Pharmacist verifies the patient name, protocol number, and recalculates the drug dose
  Pharmacist recalculates the cumulative dose and compares to the protocol total cumulative dose
Nursing procedures
  Two nurses establish the identity of the patient and the drug for administration
  Nurse verifies the drug doses against both the order sheet and the protocol
Institutional procedures
  Multidisciplinary group reviews of all new or revised protocols and preprinted orders
  Institution supports ongoing surveillance and reporting process for adverse drug events
  Institution supports continuing staff education of chemotherapy safeguards

confidential. In addition, medication errors or potential errors can be reported in confidence to the Medwatch program of the Food and Drug Administration (phone 1-800-FDA-1088 or facsimile the Medwatch form to 1-800-FDA-0178). Equally important, the ASBMT guidelines are designed to facilitate communication between physicians, nurses, pharmacists, and administrative staff to develop new safeguards and policies. Future efforts at error prevention may be further aided by enhanced monitoring and advances in bioinformatics. Using electronic medical records and computerized physician orders will help to eliminate confusing handwritten records and implementing bar coding of medications and patient identification will accurately identify patients and treatments [35].

In conclusion, this self-reporting survey of the administration of high-dose chemotherapy characterized the current practices and safety measures in a large cohort of blood and marrow transplant centers. Common themes in dose errors were cumulative drug doses given as a daily dose and nursing infusion errors. Guidelines are proposed to reduce system-wide errors and further safeguard the administration of high-dose chemotherapy and hematopoietic cell transplantation.

APPENDIX

ASBMT
ANONYMOUS QUESTIONNAIRE
(forms will be destroyed and only pooled data kept)

<u>1.   Center Specifics</u>

a.   Type of transplants (check all):
        1) Bone marrow   Peripheral blood
        2) Adult   Pediatric
        3) Autologous   Allogeneic   Unrelated

b.   Type of center: University Hospital   Research Center
                Community Hospital   University Affiliated: yes   no

c.   Year program started:

d.   Number of dedicated transplant beds:

e.   Number of transplants in: 1994   1989-1994

f.   Member of cancer group or transplant registry (check all):
        1) Cooperative Group (specify)   IBMTR   ABMTR

g.   Peer review site visit within last 3 years by:
        1) NIH   FDA   Other (Specify)

<u>2.   Chemotherapy Orders</u>

a.   Order sheets signed by (check all):
        Resident   Fellow   PA   Attending

b.   Order sheets require mandatory cosign by:
        Fellow   Attending   Not cosigned

c.   Are preprinted chemotherapy orders used?
        1) Yes   No
        2) If yes, in what percent of patients?   %
        3) Which patients do not have preprinted orders?

d.   Are preprinted orders used for each drug?   Yes   No
        1) If not, which chemotherapy is exempt?

e.   Is the protocol number specified on the orders?   Yes   No

f.   Is the drug dose (mg/m^2 or mg/kg) from the specific protocol typed on the orders?
        1) Yes   No

g.   Do preprinted orders provide specific space for:
        1) Dates of chemotherapy?   Yes   No
        2) Dose per day?   Yes   No
        3) Dose per course?   Yes   No

3.   Chemotherapy Infusions: Pharmacy

a.	Is drug ordering computerized?	Yes	No
b.	If so, does the program set dose limits?	Yes	No
c.	Does the pharmacist recalculate the dose?	Yes	No
d.	Does the pharmacist verify against protocol?	Yes	No
e.	Verification by: one pharmacist	two pharmacists	

4.   Chemotherapy Infusions: Nursing

a.	Does the nurse verify patient ID?	Yes	No
b.	Does the nurse verify dose and drug in bag?	Yes	No
c.	Does the nurse verify dose against orders?	Yes	No
d.	Does the nurse verify dose against protocol?	Yes	No
e.	Does the nurse verify weight/BSA of patient?	Yes	No
f.	Verification by: one nurse	two nurses	

5.   Quality Control

a.   Who reviews preprinted orders and revisions? (check all):
Principal investigator   Medical Director   Research Nurse
Pharmacy Director   Nursing Director   Other (specify)

b.   Do you have an active, multidisciplinary Standard Practice Committee to
update/revise orders and transplant practice? Yes   No

c.   Do you have a transplant Quality Assurance Committee? Yes   No

d.   Do other committees/groups review transplant practice? (describe)

e.   Does the IRB review all protocols? Yes   No
If no, which are exempt?

f.   Who, how and when do you monitor for regimen-related toxicities?

g.   Over the last 5 years, has there been inadvertent administration of higher than planned
doses of chemotherapy? Yes   No
1) How many patients?
2) Which agents?
3) Why did it occur (be specific):
4) How was it detected?

6.   Systems Design

a. What aspects of your system are the strongest safeguards?
b. What are areas of concern for safety?
c. Are you planning any change in your policies? Yes   No
If yes, specify:
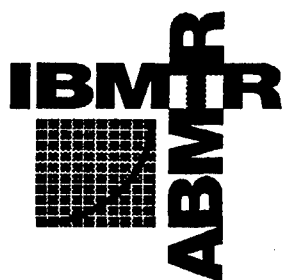
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IBMTR/ABMTR Statisticians' Manual

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IBMTR/ABMTR Statisticians' Manual

Table of Contents

I. STUDY PROTOCOLS FOR ANALYSES USING IBMTR/ABMTR DATA

The Study Protocol is an invaluable tool for performing analyses of high scientific quality that address important clinical and biologic issues in a way that most efficiently uses the data and personnel resources of the IBMTR and ABMTR. The Study Protocol is also an essential communications tool that clarifies the study objectives of Working/Writing Committee participants and ensures that they will be met by the analyses conducted at the Statistical Center. Ideally, preparation of the Study Protocol will involve as many members of the relevant Committee as possible so that important aspects of the problem under study are addressed to the fullest extent possible. Preparation of the Study Protocol is an important opportunity for Statistical Center personnel to inform Working/Writing Committee participants about the capabilities and limitations of IBMTR/ABMTR data and resources. It also offers Writing/ Working Committee participants to contribute their clinical and scientific expertise. A Study Protocol should be prepared as soon as a Study Proposal (see form in Appendix A) is approved by the relevant Working Committee. The following outline should be used, modified as necessary for the needs of particular projects. A sample Study Protocol is included in Appendix B.

A. OBJECTIVES

The aims of the study should be stated as concisely and clearly as possible. A person reading the Objectives should have clear idea of the primary issue(s) being examined. Examples are: 1. to determine whether allogeneic transplants exert a graft-versus-tumor effect in multiple myeloma; 2. to determine the safety and efficacy of autotransplants for ovarian cancer; or, 3. to compare the efficacy of allogeneic and autologous transplants for acute myelogenous leukemia in first and second remission. Collecting and analyzing data are not objectives in themselves - the objective is the purpose for which the data will be used. Consequently, objectives such as "to collect and analyze data on autotransplants for multiple myeloma" should be avoided.

B. BACKGROUND

This section, generally prepared by the Study Chair, should briefly summarize the rationale for the study, citing relevant previous work. A person reading the Background should have a clear idea of the importance of the intended study. This section gives the statistician performing the study a clearer idea of the clinical and biologic issues involved and identifies studies in the literature which examine similar issues that may provide insight for data analysis. The Background will often be prepared as part of the Study Proposal and may serve as the outline for the Introduction/Discussion of the final manuscript.

C. STUDY POPULATION

The section should clearly define the selection criteria for patients to be included in the analysis. *It should be as specific as possible,* including requirements of age, performance status, disease and disease stage, years of transplant, prior treatment (e.g. persons with CML receiving only hydroxyurea and/or interferon pretransplant), donor type, specific transplant regimens (e.g. methotrexate and cyclosporine for GVHD prophylaxis) or any other restriction relevant to the study. *It is important that these restrictions be defined prospectively based on biologic and statistical principles and not after examination of outcomes.* If the study involves combining IBMTR/ABMTR data with data from another group, the selection criteria for patients in the other database should also be specified (e.g. persons < age 40 years achieving complete remission after induction therapy for AML and receiving high-dose cytarabine for consolidation).

D. OUTCOMES

Outcomes to be studied should be defined clearly, including time-points, where relevant. Outcomes commonly analyzed are discussed in section III of this manual.

E. VARIABLES TO BE ANALYZED

This section is important in that it requires study participants to determine which relevant variables are, in fact, available in the IBMTR/ABMTR database and the format in which the data are collected. All potential outcome and explanatory variables should be listed with suggested categories for analysis. The categories to be used should be discussed with the Study Chair and other Committee members to determine that they are based on sound biological principles and consistent with previous literature. Different studies may require different degrees of detail for specific variables (e.g. conditioning regimen may be considered simply as TBI versus no TBI or as TBI + Cy versus TBI + Cy + VP16 versus Busulfan + Cy versus other specific regimen depending on the objectives of the study). For studies involving combining IBMTR/ABMTR data with data from other groups, the availability of specific variables in both databases should be confirmed. An essential consideration in this regard is the timing of specific measurements. For example, the IBMTR/ABMTR collects data on performance score at the time of transplantation while a chemotherapy database may have available data on performance score at time of diagnosis or remission - since the measurements are at different time points, they cannot be considered equivalent variables. Specifying the list of variables in detail avoids confusion about comparability of data.

If the study requires collecting supplemental data for variables not routinely collected by IBMTR/ABMTR, these variables and plans for supplemental data collection should be specified in this section (see Section IID).

F. METHODS

(1) General approach

This section should describe in non-technical terms the approach to achieving each of the objectives of the study. Data limitations and implications of potential findings may be discussed. For example, to address the objective of determining whether there is a graft-versus-myeloma effect in allografts for multiple myeloma, the general approach might be to compare relapse rates after identical twin transplants and HLA-identical sibling allotransplants for myeloma, adjusting for other factors associated with relapse. A lower relapse rate after allografts would suggest that a graft-versus-myeloma effect exists. The level of detail in this section depends on the issues being addressed and the specifics of the study population.

(2) Statistical methods

This section should include the specific methodology planned, with a discussion of its limitations if relevant. This should include estimations of the power of the analysis to achieve each of the objectives, given anticipated sample size. In contrast to prospective studies, where numbers of patients to be studied is determined by the power desired, IBMTR/ABMTR studies generally focus on a defined number of patients available in the database. The questions that can be answered, therefore, are determined by the numbers of patients available.

G. WRITING COMMITTEE PARTICIPANTS

A Writing Committee must be formed for each study, generally derived from the Working Committee sponsoring the study. Centers contributing large numbers of patients to be included in the study should be contacted to determine whether they wish to have a representative on the Writing Committee, if they have no representative on the Working Committee. If the Study involves collaboration with another Group, the Group should determine the individuals to be included in the Writing Committee. Contact information should be listed for the Study Chair and Co-chairs and the Study Statistician.

H. TIME LINE

A provisional time line for various landmarks in the study should be included. This is especially important when supplemental data must be collected (see section IID). Possible landmarks include: Preliminary analysis of patients to be studied (descriptive characteristics); preparation of supplemental data collection instrument; completion of supplemental data collection; preparation of study file; univariate analyses; multivariate analysis; first draft of manuscript.

II. STUDY FILE PREPARATION

The aim in preparing a study file is to have a study population with selected (by study design) characteristics who are consecutively treated patients at participating centers with adequate follow-up and in large enough numbers to give the analysis sufficient statistical power for its goals. The IBMTR and ABMTR collect data on two levels: *Registration* data and *Research* data. All participating centers *register* consecutive transplants with basic data (age, sex, disease, disease stage and duration, graft type, donor type, conditioning regimen, graft treatment, GVHD prophylaxis and posttransplant disease status, survival, second cancers and primary cause of death). Many centers also also submit detailed data collection forms (Report Forms) with comprehensive clinical and demographic data on a subset of these cases, determined by the Statistical Center and based on needs for current and anticipated studies. Data from Report Forms are entered in the *Research* database. *Registration* data allow analysis of trends in transplant use and outcome and identification of patients for specific studies. Study files, however, generally are generated from the *Research* database.

A) DATA SELECTION

(1) Case Selection

Cases to be analyzed in a specific study will be determined through discussions between the statistician and the Study Chair. As stated in the guidelines for preparing Study Protocols, selection criteria should be defined prospectively based on biologic and statistical principles **not** after the examination of outcomes. The study population is usually limited by disease and type of transplant (either allogeneic or autologous). Other common restrictions include year of transplant, age at transplant, disease stage at transplant, and donor type and tissue type for allogeneic transplants. Restrictions should be applied to the database one at a time with the most important restrictions first and the number of available patients recorded after each restriction is added. Restrictions that result in a study population too small for sufficient statistical power may be liberalized if this would not compromise the scientific goals of the study.

A common problem in case selection is handling cases missing the information used to restrict the population. Whether or not these patients should be excluded should be discussed with the study chair. This results most frequently when the variable is one that has not been collected on all versions of the data collection forms (Report Forms). Discussion should focus on number of cases available for analysis, the number of patients missing the information and the potential biases that may be introduced by excluding these patients. It may be necessary to contact centers reporting these patients to request missing information. Supplemental questionnaires may be designed to capture this information.

(2) Sequential Reporting

IBMTR/ABMTR policy states that all patients who begin their high-dose therapy (conditioning) must be registered with the IBMTR/ABMTR even if for some reason they do not receive their graft. A sequential numbering system (IUBMIDs) must be developed at each center, with each patient numbered consecutively at the time high-dose chemotherapy begins.

While the IBMTR/ABMTR conducts audits annually on randomly selected teams to verify sequential reporting , the statistician should also check for sequential reporting for each center with patients included in the study file. One method to check for sequential reporting is to sort all cases (regardless of disease) by IUBMID. A separate report should be generated for each center. The list of patient identifiers (IUBMID) should be consecutive with no large time intervals between transplant dates. It should be remembered that most but not all teams have separate numbering systems for autologous and allogeneic transplants. Any indication of non-consecutive reporting should be verified by the Communications Coordinator. Centers are required to *register* consecutive patients but are not required to *report* all cases; cases classified (by the Statistical Center) as exempt from reporting are indicated by the variable EXEMPT.

Centers with breaks in sequential reporting should be brought to the attention of the Scientific Director. The center will be contacted and a plan developed to help the team comply with the IBMTR/ABMTR policy of sequential reporting. **All** cases from centers with non-consecutive reporting should be deleted from the analysis, after discussion with the Scientific Director and Study Chair.

(3) Variable selection

Before preparing the study file, the statistician should work closely with the Study Chair to prepare a list of all variables required for analyses which were included in the Study Protocol (see chapter I). Variables will include patient, disease and transplant characteristics and outcome variables (both time intervals and events). The list may be modified after input from the Writing Committee when the Study Protocol is circulated.

For patients with multiple transplants, pretransplant data from the first transplant are generally selected for analyses, while posttransplant data will include both first transplant outcomes and 'global' variables which reflect outcome from all transplants. **In general**, the engraftment, GVHD, infection and posttransplant disease status variables used are those which reflect events after the first transplant, while survival includes the patient's experience through all transplants. The date of second and subsequent transplants should be included in all study files.

B) FOLLOW UP

While most IBMTR/ABMTR analyses use data captured on Report Forms and stored in the *Research* database, the survival, relapse/progression status and dates of relapse/progression and last contact in the research database may not be the most recent available because of delays in follow-up Report submission and entry. Update requests for previously registered cases are distributed approximately every six months and the updated information is added to the *Registration* database. Additionally, survival and disease status information from each follow-up Report Form is added to the *Registration* database as part of the log-in procedure, before the entire Report is keyed into the *Research* database. To use the most recent survival and relapse/progression information on each patient in analyses, last contact data from the *Registration* database must be merged into the *Research* database. The following SAS statements are used to merge two data sets, called *dreg* and *drep*, by TEAM and IUBMID:

> PROC SORT DATA=DREG; BY TEAM IUBMID;
> PROC SORT DATA=DREP; BY TEAM IUBMID;
> DATA MERGED;
> MERGE DREG DREP; BY TEAM IUBMID;

Note: The data sets must each be sorted by TEAM and IUBMID before merging.

While the variable names for survival status and survival interval are the same in the *Registration* and *Research* databases, the variables must be renamed in one of the data sets and values compared after merging. (Survivals should never be shorter in the *Registration* database.) A new SAS data set containing the updated survival information can then be created.

IBMTR/ABMTR rules require follow-up through death or 100 days (whichever occurs first) and yearly or at time of death thereafter. Follow-up on patients who die after transplant may be received more quickly than follow-up on patients still alive after transplant. This can lead to survival probabilities appearing worse than they actually are, especially for the more recent years. The purpose of the steps listed below is to ensure that, during the study period selected, patients both alive and dead after transplant have equivalent follow-up. The following steps help identify incomplete reporting:

1. Update patient status using *Registration* data through a chosen date (i.e. patient alive or dead on this day). A patient who dies after the chosen date is considered alive for the current analysis. In general this date should be one year before the study file is prepared to allow adequate time for follow-up to be reported and entered.

2. Create a variable for each patient called TIMEFU for the time between date of last contact and the chosen date. Have the Communications Coordinator request updates on surviving patients with TIMEFU > 12 months.

3. Identify teams, if any, with large proportions of patients with no recent follow-up. These should be contacted in a separate communication (FAX or phone) to determine whether follow-up can be provided in a timely manner for the patients in the study. If not, all patients from these center should be excluded from the study.

4. To identify teams with inconsistencies in the follow-up of dead and living patients the following SAS statements can be used. The median, range and five highest and lowest values and a frequency table for TIMEFU will be printed in the output by team for dead and alive patients:

> PROC UNIVARIATE FREQ;
> VAR TIMEFU;
> BY TEAM DEAD;

For each team, compare values of variable TIMEFU for dead and alive patients. Since most transplant deaths occur early, TIMEFU should be longer for dead than alive patients. Centers that have, in general, shorter TIMEFUs for dead than living patients may be preferentially reporting deaths. These teams should be investigated further to determine whether this is true and brought to the attention of the Scientific Director. If adequate follow-up on survivors cannot be obtained, all patients in the center should be excluded from analysis.

C) DATA REVIEW

(1) Missing Values

All variables in the study file should be reviewed for missing values before analyses begin. Patients with missing values for key variables may need to be excluded. Missing values result from three causes:

1. Data not requested: data not collected on an older version of a Report Form
2. Data unknown: Center indicates data not known e.g. HSV serology not tested.
3. Data not reported: Item not completed on Report Form.

One way to view the scope of missing data problems, is to create a column titled 'N evaluable' on tables for the Writing Committee. The statistician and Study Chair can review the initial tables and make a plan to address the problem, if necessary. If values for a particular variable are missing for a large percentage of the study population and the variable is not a key one, the variable may be dropped. Alternatively, a related variable which provides similar information may be substituted. In cases where the missing values are critical, the center may be contacted if the missing data falls into categories 1 or 3 above.

(2) Outlier Assessment

Before analyses can begin, data for all patients must be reviewed to determine that all data points appear reasonable. Each dependent and independent variable included in the study file must be checked. Values should fall within expected ranges and all negative values flagged. One way to look for outliers is to use PROC UNIVARIATE in SAS. The following statement will give, along with other information, the median, range, 5% and 95% quantiles, and a stem and leaf plot for DEPVAR1:

```
PROC UNIVARIATE FREQ PLOT;
VAR DEPVAR1;
```

Values above the 95% quantile and below the 5% quantile should be discussed with the Study Chair to determine if the values are appropriate. In some cases, cross tabulations among related variables should be done. The Study Chair can act as a resource in these matters. Report Forms of patients with outliers should be reviewed. In some cases the information may have been entered incorrectly, or the data manager may have made a note in the margin of the Report with an explanation of the value. There may also be attached letters and comments at the end of a Form with further details. When reviewing the Form, also look at the back of the last page to see if the team has been contacted regarding this matter. The team may have already responded to a previous request by the IBMTR/ABMTR regarding the variable. The Communications Coordinator may have recent letters regarding outliers that have not yet been processed and attached to the Report Forms. Finally, it may be necessary to contact the center that completed the Report Form to verify the value in question (see section II.D).

(3) Variables with 'Other' categories

Data collection forms change as technology changes and new drugs and procedures are developed. Some studies may include patients with data collected on older versions of the Report Form. When a drug or procedure is rare, the response to a question may be put into an 'other' category with a space provided to write in the specific information. As the drug comes into frequent use, a new category is created on a new version of the Report Form. At times data in these "other" categories will be needed for analyses. Currently, these data are entered as text field and are retrievable from the database. In the past, only the "other" or a few prespecified categories of "other" were entered. If it is necessary to know what the "other" was, the statistician must work with the Manager of Information Systems to assign personnel to extract and enter this information from the Report Forms.

D) INTERACTION WITH TEAMS

It is sometimes necessary to communicate with Individual centers in preparing a study file. Reasons include:

1. Missing data
2. Data discrepancies/outliers
3. Need for supplemental data not collected on current Report Forms

For discrepancies and missing data, the Communications Coordinator usually contacts the individual center regarding these matters via letter or fax. The following information should be included with each request to facilitate response by the center: registry, Registry ID number, Team number, IUBMID, disease, birth date, and transplant date. For missing data, provide the specific Report Form number, page and item number. For discrepancies and outliers, provide the specific Report Form number, page, item number and the specific question you want answered. If several teams involving many patients must be contacted regarding the same variable, please create worksheets for each center, suitable for faxing, listing the patient information cited above, and space for the team to write in the response. The sheets should be titled with the specific project name and full center name at the top of the page. If a center is responding about multiple patients, the number of patients for each team should be given at the end of each team worksheet. A draft of a letter to the team, to be enclosed with the worksheet, should also be given to the Communications Coordinator. The brief letter should state the project name and purpose of the request, what data are required and the date by which the data are required.

New or more specific data, not collected on the Report Form, is sometimes required for all patients in the study. For a single item, the method described above for obtaining responses for the same variable from multiple teams should be used. Worksheets should be created for every team and a letter drafted, to be included with each worksheet.

Some studies require a supplemental data collection form to be prepared to collect information on new topics involving multiple questions, and dates. The statistician should work closely with the Study Chair and with Manager of Information Systems in designing the new supplemental form. After an initial draft is completed, the draft should be distributed to the rest of the Working Committee for comments and piloted by several data managers to ensure that the responses are as expected. Once the final form is available, it should be given to the Communications Coordinator along with worksheets for every team and a draft of a letter to be included with each worksheet as described above.

E) DATABASE CORRECTIONS

Whenever a team responds with missing data or resolves a discrepancy, the Form must be corrected with red ink, your initials and date noted, and the letter or fax from the team attached to the form. The Report Form is then forwarded to the Systems Coordinator with a note specifying the data base change. (Some changes need physician review before the change is incorporated in the database; this is the responsibility of the Systems Coordinator.)

It may be necessary to also make these changes directly to the study file ('hard code' the changes) if analyses are proceeding quickly. There will be a lag between the time the Systems Coordinator receives the changes and the time an updated database retrieval with the appropriate changes is made.

III. INTERMEDIATE AND TERMINAL EVENTS USED IN STUDIES

A) GENERAL OUTCOMES

(1) Engraftment

Neutrophil Recovery -- defined for separate targets of either ≥ 500 or ≥ 1000 neutrophils/mm^3 as the time to achieve the specific indicator (NEUT5 or NEUT10). The interval variables are INTXNT5 and INTXNT10, respectively, which are measured in days. The interval for a patient who has not achieved the specific indicator is equal to SURVDAYS. This event is summarized by the cumulative distribution function (1-Survival curve).

Platelet Recovery -- defined for separate targets of either $\geq 20,000$, $\geq 50,000$ or $\geq 100,000$ platelets/mm^3 as the time to achieve the specific indicator (PLAT20, PLAT50 or PLAT100). This event is evaluable at 7 days from the last platelet transfusion. The interval variables are INTXP20, INTXP50, INTXP100, respectively, which are measured in days. The interval for a patient who has not achieved the specific indicator is equal to SURVDAYS. This event is summarized by the cumulative distribution function (1-Survival curve).

Graft failure -- Failure to achieve neutrophils ≥ 500/mm^3 or achievement of ≥ 500 neutrophils/mm^3 followed by a decrease to <500/mm^3. The indicator variable is REJECT and the interval variable in INTXFAIL, which is measured in months. The interval for a patient who never achieves neutrophils ≥ 500/mm^3 is 0.03. The interval for a patient who achieves ≥ 500/mm^3 and then has a decrease is the first day the neutrophils are <500/mm^3. The interval for a patient who does not have graft failure (REJECT=0) is equal to INTXSURV. This event is summarized by the cumulative distribution function (1-Survival curve).

(2) Graft-versus-host disease (GVHD)

Acute GVHD -- development of Grade I-IV acute GVHD. The time of first attainment of acute GVHD is the event time even if the maximum grade occurs later. Patients are at risk for this event at 21 days after transplant, if they have evidence of engraftment. In most analyses patients with a grade of II-IV are considered to have acute GVHD and patients with a grade of 0-I are not considered to have acute GVHD. The indicator variable for any Grade II-IV GVHD is AGVHIX1. A variable which indicates both the presence and severity of acute GVHD is AGVH1. The interval variable is DATXAGV1, measured in days. In some studies, particularly those involving donors other than HLA-identical siblings, the incidence of grade III-IV AGVHD is of interest. This indicator variable is AGVHIX34. The interval variable is DATXAG34, measured in days. The interval for a patient who has not achieved the specific acute GVHD indicator is equal to SURVDAYS. This event is summarized by the cumulative distribution function (1-Survival curve).

Chronic GVHD -- development of any chronic GVHD. The time of first attainment of chronic GVHD is the event time. Patients are at risk for this event at 90 days after transplant. The indicator variable for any chronic GVHD is CGVHIX1. The interval variable is INTXCGV1, measured in months. The interval for a patient who has no chronic GVHD is equal to INTXSURV. This event is summarized by the cumulative distribution function (1-Survival curve).

(3) 100 Day Mortality

This event is death prior to 100 days posttransplant. Patients alive at last observation with less than 100 days of follow-up are not considered at risk for this event. The relevant data for this event is a binary variable, MORT100, with the value 1 if they die prior to 100 days and 0 if they are alive at day 100. This event is summarized by the estimated probability of surviving 100 days.

(4) Survival

The variable which indicates which individuals die is SURVHI. The codes 1 and 3 correspond to censored observations. The code 2 corresponds to a death. The time to death (or last contact for survivors) is represented in the variable INTXSURV, measured in months. Patients are at risk for this event at the time of transplant. The event is summarized by a survival curve.

B. LEUKEMIA-SPECIFIC OUTCOMES

(1) Treatment-related Mortality (also called Transplant-related Mortality or Non-relapse Mortality)

This event is defined as death in continuous remission. Patients who relapse or have persistent leukemia are considered censored for this event. The time to the event is coded in the variable INTXRHI, measured in months. For a censored patient without relapse or persistent leukemia, the interval interval is equal to INTXSURV. The variable TXMORT is the event indicator with a code of 1 reflecting death without disease and a code of 0 reflecting a censored observation. Patients are at risk for this event at the time of transplant This event is summarized by the cumulative distribution function (1-Survival curve).

(2) Relapse

This event is defined as a clinical relapse of leukemia. Patients who die without disease are considered censored for this event. The time to the event is coded in the variable INTXRHI, measured in months. For a patient who has not relapsed the interval is equal to INTXSURV. For patients who receive a transplant while not in remission and do not achieve remission the time to the event is set at INTXRHI=0.03 months. The variable REALAPS is the event indicator with a code of 1 reflecting relapse and a code of 0 reflecting a censored observation. Patients are at risk for this event at transplant. This event is summarized by the cumulative distribution function (1-Survival curve).

Some patients, particularly those with chronic myelogenous leukemia, may have recurrence or persistence of a chromosome or molecular marker of their disease without clinical relapse. In most but not all studies, these patients are treated as being in remission until clinical evidence of leukemia develops. A discussion of the definition of relapse with the Study Chair should precede analysis of this variable.

(3) Leukemia -Free Survival (sometimes called Disease Free Survival)

This event corresponds to treatment failure. It is defined as death or relapse. The time to this event is the minimum of the death and relapse time and is coded in the variable INTXRHI, measured in months. For a patient who is alive in remission the interval is equal to INTXSURV. The variable LFS is the event indicator with a code of 1 reflecting death or relapse and a code of 0 reflecting a censored observation. Note that one should check that LFS=TXMORT+REALAPS. Patients are at risk for this event at the time of transplant. The event is summarized by a survival curve.

C. LYMPHOMA AND SOLID TUMOR SPECIFIC OUTCOMES

(1) Treatment Related Mortality

In general the definition is the same as for leukemia, i.e. death in continuous remission. However, lymphoma and solid tumors, even if cured, may take some time to resolve after transplant. Additionally, tests done to evaluate the status of these diseases may not be done for some time after transplant. Consequently a patient may die before the status of the lymphoma or solid tumor is determined. Any death occurring in the first 28 days after transplantation for a lymphoma or solid tumor is considered to be treatment related. Deaths occurring in the next 72 days are assumed to be treatment-related if the disease status is reported as unknown or not evaluable. The latter cases should be reviewed by the Study Chair. The indicator variable is TXMORTL with a value of 0 for censored cases and a value of 1 for patients reflecting treatment-related mortality. The interval variable is INTXREL, which is the time to relapse or death in remission, measured in months. For patients who are censored alive, INTXREL is equal to INTXSURV.

(2) Progression

This event is defined as an increase in the size of sites of known disease or development of new sites of disease after transplant. It may follow a period of "stable" disease where the lymphoma or solid tumor has < 50% reduction in known sites of disease but not new sites of disease and no increase of disease at any site. It may follow a partial remission where the tumor had a 50-99% reduction in size with no new sites of disease. It may follow a complete remission. Any recurrence of tumor or increase in size of tumor after a complete or partial remission is considered progression, even if the extent of tumor is less than pretransplant. Patients who die without progression (may have stable disease, partial or complete remission) are considered censored for this event. The time to the event is coded in the variable INTXPROG, measured in months. For censored patients the variable INTXPROG is equal to INTXSURV. The variable PROGRESS is the indicator of progression with a value of 1 reflecting progression and a value of 0 denoting a censored observation. Patients are at risk of this event 28 days after transplant. This event is summarized by the cumulative distribution function (1-survival).

(3) Progression- Free Survival

This event is defined as death or progression. The time to this event is the minimum of the death and the progression times. The time to the event is coded in the variable INTXPROG, measured in months. For patients who have not progressed, INTXPROG is equal to INTXSURV. The variable PFS is the event indicator with a value of 1 reflecting death in the first 28 days posttransplant or death or progression after day 28 posttransplant. A code of 0 denotes a censored observation. Patients are at risk for this event at the time of transplant. This event is summarized by a survival curve.

(4) Relapse (Or Recurrence)

This event is defined as clinical recurrence of disease after a posttransplant remission. *For patients transplanted in remission or for patients who achieve a complete remission after transplant,* recurrence is the same as progression. The interval is coded in the variable INTXREL, measured in months. The variable RECUR is the indicator of recurrence with a code of 1 reflecting relapse and a code of 0 reflecting a censored observation. Patients transplanted in remission or who achieve remission after transplant are at risk after 28 days posttransplant for this event. This event is summarized by the cumulative distribution function (1-Survival curve).

(5) Disease-Free Survival

The event is defined as death or recurrent disease. The time to this event is the minimum of the death and relapse times, where patients who never have a complete remission posttransplant are considered to experience the event at day 1. The time is coded in the variable INTXREL, measured in months. The variable DFS is the event indicator with a code of 1 reflecting the event has occurred and a code of 0 reflecting a censored observation. The event is summarized by a survival curve.

TABLE OF VARIABLE NAMES

Variable	Indicator (values)	Interval From Transplant (units)
Engraftment		
500 neutrophils/mm³*	NEUT5 (0,1)	INTXNT5 (days)
1000 neutrophils/mm³*	NEUT10 (0,1)	INTXNT10 (days)
20,000 platelets/mm³*	PLAT20 (0,1)	INTXP20 (days)
50,000 platelets/mm³*	PLAT50 (0,1)	INTXP50 (days)
100,000 platelets/mm³*	PLAT100 (0,1)	INTXP100 (days)
Graft Failure	REJECT (0,1)	INTXFAIL (months)
GVHD		
Acute GVHD grade 0-4	AGVH1 (0,1,2,3,4)	DATXAGV1 (days) or INTXAGV1 (months)
grade 0,1 vs 2,3,4	AGVHIX1 (0,1)	DATXAGV1 (days) or INTXAGV1 (months)
grade 0,1,2 vs 3,4*	AGVHIX34 (0,1)	DATXAG34 (days) or INTXAG34 (months)
Chronic GVHD grade 0,1,2,4	CGVH1 (0,1,2,4)	DATXCGV1 (days) or INTXCGV1 (months)
grade 0 vs 1,2,4	CGVHIX1 (0,1)	DATXCGV1 (days) or INTXCGV1 (months)
100 Day Mortality		
100 day mortality*	MORT100 (0,1)	
Survival		
Vital Status	SURVHI (1,2,3)	INTXSURV (months)
Leukemia-Specific Outcomes		
Treatment-related mortality	TXMORT (0,1)	INTXRHI (months)
Relapse	REALAPS (0,1)	INTXRHI (months)
Leukemia-free mortality	LFS (0,1)	INTXRHI (months)
Lymphoma and Solid Tumor Specific Outcomes		
Treatment-related mortality*	TXMORTL (0,1)	INTXREL (months)
Progression*	PROGRESS (0,1)	INTXPROG (months)
Relapse/Recurrence*	RECUR (0,1)	INTXREL (months)
Disease-free survival*	DFS (0,1)	INTXREL (months)

* Variable is NOT currently coded in retrieval; must be computed in study file

IV. DESCRIPTIVE STATISTICS

Descriptive statistics are used to summarize the characteristics of a data set. They are used to check for outliers, to test for differences in the study population when a hypothesis testing model is to be built and to help in discretizing continuous covariates for use in future analyses.

A) DISCRETE COVARIATES

For the discrete covariates, we calculate the number and percentage of patients for each category. In a hypotheses testing study the chi-square test is used to check whether the covariate has same distribution for all levels of the main effect.

Summary statistics and tests are performed using the SAS procedure FREQ. For example, the following SAS procedure will yield the number and percentage of males and females for each treatment group, and *p-value* of the chi-square test:

PROC FREQ; TABLES SEX*GROUP / CHISQ;

When the sample size is small relative to the size of a contingency table, chi-square test may not be a valid test. In this case SAS will print a warning message that the chi square test is not valid. In such a case, Fisher's exact test is a more appropriate test. We then change "chisq" option to the option "exact" in the SAS code which will give us the *p-value* of Fisher's exact test.

B) CONTINUOUS COVARIATES

For continuous covariates we report, in writing committee memos or maunuscripts, medians and ranges for the variable. For discussion at statistical staff meetings or with the clinical investigator, we use the SAS procedure PROC UNIVARIATE to compute summary statistics that allow us to check for outliers. The coding for this procedure for a covariate age is

PROC UNIVARIATE PLOT FREQ; VAR AGE;

This command will produce summary statistics (mean, median, range, standard deviation, etc.), a stem-and-leaf plot or a histogram, and the estimated frequencies for each value of the variable. To identify outliers one could add the statement ID PATIENTNO; , for example, where PATIENTNO is some identifier of the patient. This will associate the value of PATIENTNO with the values UNIVARIATE prints for the five largest and smallest observations. Using a BY variable, one can have SAS produce a UNIVARIATE analysis for each level of the factor of primary interest in a hypothesis testing study.

When the goal of the study is to compare outcomes between treatment groups, the Kruskal-Wallis test is used to check if the distribution of a continuous factor is the same over the groups. The SAS procedure used is PROC NPAR1WAY which is coded as follows:

PROC NPAR1WAY WILCOXON; CLASS GROUP; VAR AGE;

C) FOLLOW-UP TIME

To compare the survival probabilities, we need to study the follow-up time. We use the product-limit estimator proposed by Kaplan-Meier to estimate the probability of the follow-up time, and log-rank test to test if the cohorts have same probability of follow-up times. To do so, let TIME be the time of event or end of follow-up, and STATUS be the indicator of censorship; that is STATUS=1 if patient is still alive; 0 otherwise. Note that here we are coding deaths as censored observations and usual censored observations as events since we are trying to estimate the distribution of the on study times if patients had not died.

The SAS procedure LIFETEST will estimate the probability distribution of the follow-up time, the median follow-up time, the range of follow-up times (largest and smallest on study times) and *p-value* of the log-rank test which is used to check for differences between groups:

PROC LIFETEST; TIME TIME*STATUS(0); STRATA GROUP;

D) SURVIVAL

The survival curves are useful for preliminary examination of the data, for computing the common interested quantities such as median survival time or the probability of survival at some point in time, and for evaluating the fit of regression models. The standard tests for comparing survival curves across the different treatment groups are important for analyzing the data. In survival analyses the time to event data could be censored and/or truncated. Here we only discuss the methods involving right censored time to event data. For other type censored or truncated data see Klein and Moeschberger (1997).

(1) Summary Curves

The standard estimator of the survival curve is the product-limit estimator which was proposed by Kaplan-Meier (1958), and is often called the Kaplan-Meier estimator or the actuarial estimate. The variance of the product-limit estimator is estimated by Greenwood's formula. The SAS's PROC LIFETEST procedure provides this estimates of survival functions and it's standard error. Let TIME be the event time and STATUS be indicator of the noncensorship, that is, STATUS=1 if event occurred and 0 otherwise. The SAS codes are

```
PROC LIFETEST;
TIME TIME*STATUS(0);
```

This command will produce the summary survival curve. To make plots of the survival curves an output data set can be produced which contains the survival estimates and their standard errors. An example of the coding is as follows:

```
PROC LIFETEST DATA=TEMP NOPRINT
OUTSURV=PLOTME;
TIME INTXRHI*NLFS(0);
STRATA DISPX;
```

This coding produces the data set TEMP which contains the following variables:

DISPX -- The stratification variable
INTXRHI --The time variable
CENSOR -- The indicator of censoring (1-censored, 0-dead)
SURVIVAL --The estimate of the survival function at time INTXRHI in strata
            DISPX
SDF_LCL SDF_UCL -- 95% Naive confidence interval for the survival function
STRTUM -- Strata number

Note that for a censored observation the values for the confidence interval are missing.

To plot the survival curves the following code could be used. In this case there are 5 levels to the variable DISPX. We will create variables S1, ..., S5 which have the estimates for the respective strata. (In the data statement the variables R1, ..., R5 are the estimates of 1-SURVIVAL used when drawing graphs for relapse curves). To Indicate a censored observation we will put the symbol "I" at each censored observation. The values of the survival function at the

censored observation are coded in CS1, ..., CS5 (CR1, ... , CR5 for relapse). The data set revised is used in plotting.

```
DATA REVISED; SET PLOTME;
IF _STRTUM_=1 THEN DO;
   S1=SURVIVAL;
   R1=1-SURVIVAL;
   IF _CENSOR_ = 0 THEN CS1=.;
   ELSE DO; CS1=S1;  CR1=R1; END;
   END;
ELSE IF _STRTUM_=2 THEN DO;
   S2=SURVIVAL;
   R2=1-SURVIVAL;
   IF _CENSOR_ = 0 THEN CS2=.;
   ELSE DO; CS2=S2;  CR2=R2; END;
   END;
ELSE IF _STRTUM_=3 THEN DO;
   S3=SURVIVAL;
   R3=1-SURVIVAL;
   IF _CENSOR_ = 0 THEN CS3=.;
   ELSE DO; CS3=S3;  CR3=R3; END;
   END;
ELSE IF _STRTUM_=4 THEN DO;
   S4=SURVIVAL;
   R4=1-SURVIVAL;
   IF _CENSOR_ = 0 THEN CS4=.;
   ELSE DO; CS4=S4;  CR4=R4; END;
   END;
ELSE IF _STRTUM_=5 THEN DO;
   S5=SURVIVAL;
   R5=1-SURVIVAL;
   IF _CENSOR_ = 0 THEN CS5=.;
   ELSE DO; CS5=S5;  CR5=R5; END;
   END;
```

PROC GPLOT is used to draw the graph. We are plotting 10 curves so 10 SYMBOL statements are needed. For the first 5 a step function is drawn. These are the curves S1,. .., S5. For the next 5, no curve is drawn. Only the symbol I is plotted.

```
PROC GPLOT DATA=REVISED;
SYMBOL1 REPEAT=5 COLOR=BLACK I=STEPLJ V=NONE W=1 L=1;
SYMBOL2 R=5 COLOR=BLACK I=NONE F=SWISS V='I';
PLOT (S1 S2 S3 S4 S5 CS1 CS2 CS3 CS4 CS5)*INTXRHI/OVERLAY;
RUN;
```

(2) Comparisons of Survival Curves

If two different treatments are given to two groups separately, one of the most important questions would be "Did two treatments make a difference in the probability of survival?". To answer this question, we need to test the null hypothesis that the survival functions are same across the two treatment groups, that is H_o: $S_1(t) = S_2(t)$, for all t, where $S_1(t)$ and $S_2(t)$ are the survival functions for treatment group 1 and 2 separately. We use a log-rank test for testing this null hypothesis (see Klein and Moeschberger Section 7.3). The SAS codes for the log-rank test are

```
        PROC LIFETEST;
        TIME TIME*STATUS(0);
        STRATA GROUP;
```
Note that the "TEST" statement in PROC LIFETEST is **not** used here.

The above test is a comparison of the entire survival curves. Occasionally we wish to compare two curves at a fixed point in time, T_0. To perform this test the following statistic is used

$$Z = \frac{S_1(T_0) - S_2(T_2)}{\sqrt{V[S_1(T_0)] + V[S_1(T_0)]}} \; ,$$

where $V[S_k(T_0)]$ is the estimated variance of the Kaplan-Meier Estimator for group k, k=1,2. This test is typically done by hand on a calculator using the output of PROC LIFETEST.

(3) Confidence Intervals for Survival function

As noted above the output data set from PROC LIFETEST contains a 95% confidence interval for the survival function. Recent statistical literature suggests that these intervals are suspect for small to moderate samples. A better way of constructing intervals is to use the log transformed intervals (Klein and Moeschberger Section 4.3). The formula for these intervals is as follows

$$(S(t)^{1/\theta}, S(t)^{\theta}) \text{ where } \theta = \exp\left\{ \frac{Z_{1-\alpha/2}\,\sigma(t)}{\ln[S(t)]} \right\}, \text{ and } \sigma^2(t) = V[S(t)]/S(t)^2.$$

Using the output data set from LIFETEST a 95% confidence interval can be computed as follows:

```
        DATA NEW; SET OLD;
        SE=(SDF_UCL- SDF_LCL)/(2*1.96*SURVIVAL);
        THETA=EXP(1.96*SE/LOG(SURVIVAL));
        LOWER=SURVIVAL**(1/THETA);
        UPPER=SURVIVAL**THETA;
```

Note that the confidence intervals constructed in this manner are pointwise intervals.

E) 100 Day mortality

When analyzing bone marrow transplant data it is sometimes important to study 100 day mortality. In the research database, virtually all patients either died within 100 days or had follow-up time longer than 100 days since 100 days of follow-up is required for the initial report form. In the registration database, there are some cases with follow-up time less than 100 days. However, the percentage of such cases is very small (less than 1%). For those patients with follow-up times · less than 100 day,s whether they will die within 100 days is unknown. We exclude these cases when analyzing the 100 day mortality rate. We use a chi-square test to test whether the 100 day mortality rates are same across the treatment groups. Define the variable Z=1 if patients died within 100 days and 0 otherwise. The SAS codes are

```
        PROC FREQ; TABLES Z*GROUP / CHISQ;
```

V MULTIVARIATE MODELS FOR SURVIVAL

In this section we discuss statistical procedures for modeling multivariate survival. Mutivariate survival modeling is used in two related situations: The first is the situation where we wish to compare two or more groups after making adjustments for other factors which may influence outcome. The second is where we wish to determine which risk factors may be related to a given outcome. We shall term these hypothesis testing and exploratory model building analyses, respectively.

A. Definitions

Factors

The analysis to be performed is a regression analysis where the endpoint is the time to some event (See Section III for a definition of the event times). The time to event is called the dependent variable. Explanatory information is contained in a set of *factors*. A factor is a set of explanatory covariates that describes a particular attribute of the patient being transplanted. Associated with a factor is a degree of freedom. The *degree of freedom* is the number of independent variables which make up the factor.

When the phenomena under consideration is categorical with k categories, then the factor consists of k-1 binary covariates with each indicating a given level of the covariate (one level is the baseline so only k-1 levels are needed). It should be noted that the coding within a factor is not unique, since any one of the k levels can be used as the baseline. However, when making an inference about a factor any of the equivalent codings will give rise to the same conclusion.

As an example consider the coding of a factor which represents the sex of the donor and recipient of an Allo transplant. This factor will have three degrees of freedom and require the definition of three binary covariates. One coding, which has the male donor and male recipient (M->M) as the baseline is:

$$Z_1 = \begin{cases} 1 \text{ if } F\text{-> } F \\ 0 \text{ otherwise} \end{cases}$$

$$Z_2 = \begin{cases} 1 \text{ if } F\text{-> } M \\ 0 \text{ otherwise} \end{cases}$$

$$Z_3 = \begin{cases} 1 \text{ if } M\text{-> } F \\ 0 \text{ otherwise} \end{cases}$$

An alternate coding (with the same baseline is)

$$Z_1 = \begin{cases} 1 \text{ if Female donor} \\ 0 \text{ otherwise} \end{cases}$$

$$Z_2 = \begin{cases} 1 \text{ if Female recipient} \\ 0 \text{ otherwise} \end{cases}$$

$$Z_3 = \begin{cases} 1 \text{ if Female Donor and Recipient} \\ 0 \text{ otherwise} \end{cases}$$

Other examples of factors are as follows:

Factor	Coding	Degrees of Freedom
Age as a continuous factor	$Z = Age$	1
Age Categorized into 0-10[1],10-20,>20	$Z_1= \begin{cases} 1 \text{ if } 10<Age\leq20 \\ 0 \text{ otherwise} \end{cases}$ $Z_2= \begin{cases} 1 \text{ if } Age>20 \\ 0 \text{ otherwise} \end{cases}$	2
Year of Transplant[2] (Patients transplanted in 87-92)	$Z_1= \begin{cases} 1 \text{ if } 88 \\ 0 \text{ otherwise} \end{cases}$ $Z_2= \begin{cases} 1 \text{ if } 89 \\ 0 \text{ otherwise} \end{cases}$ $Z_3= \begin{cases} 1 \text{ if } 90 \\ 0 \text{ otherwise} \end{cases}$ $Z_4= \begin{cases} 1 \text{ if } 91 \\ 0 \text{ otherwise} \end{cases}$ $Z_5= \begin{cases} 1 \text{ if } 92 \\ 0 \text{ otherwise} \end{cases}$	5

1) 0-10 baseline
2) 87 Baseline

Factors can be either *fixed time* or *time dependent* factors. A fixed time factor is one whose value is know at the time of transplant (or at the "zero" time of the study). Examples of fixed time factors are year of transplant, preparative regimen, age, sex, GVHD prophyaxis, etc. Fixed time covariates are dealt with in Chapter 8 of Klein and Moeschberger

Time dependent factors are those whose values are not known at the time of transplant. These may be measurements taken at some planned point after transplant, (e.g. Karnofsky score at 6 months post transplant), the occurrence of intermediate events (e.g., occurrence of acute GVHD, platelet recovery time, etc.), events which happen at some time after transplant (e.g. second transplant), or artificially created (e.g., factors used to check model assumptions or factors to adjust for non proportional hazards (See V.C below)).

Censoring and Truncation

Right censoring occurs when at the last observation of the subject the event under study has not yet occurred. This may be because either the patient is still alive and disease free at their last observation time, because the patient was lost to follow-up, or because some other event not under study occurred. Censored data is partial information about the timing of the event of interest in that all we know is that for this patient the event has yet to occur at the last time we saw the patient. The following table summarizes censoring for some common events we study.

Event of Interest	Patient Status at last follow-up which leads to censoring
Death	Alive
Relapse or Progression	Alive and Disease free Dead without Disease
Treatment related mortality	Alive and Disease Free
Acute GVHD	Dead without acute GVHD Alive without acute GVHD
Chronic GVHD	Dead without chronic GVHD Alive without chronicGVHD

Left Truncation occurs when some intermediate event must occur before the patient becomes at risk to experience the event in which we are interested. That is when the event time, X, is measured from some landmark but only subjects who experience some intermediate event at time, V, are to be included in the study. This is the case, for example if we wish to draw inference about X, the time from transplant to death or relapse, for those patients whose platelets have recovered to a self sustaining level. If V is the time until platelets recover for the patient, then only patients who experience this intermediate event are entered into the study. Life lengths in this study will be left truncated. The times V are sometimes called *delayed entry times..*

Left truncation also occurs when we are comparing patients given a transplant to those given chemotherapy. Since we only observe patients who were transplanted in our data base, if the "zero" point is the time of diagnosis, then our patients are not a risk to die until they are transplanted and as such they are left truncated at the time of transplant. Section 9.4 of Klein and Moeschberger discuss left truncation.

Cox Regression Model and Relative Risks

The basic model for analysis is the proportional hazards model or the Cox regression model. For this model the hazard rate for an individual with set of covariates $(Z_1(t), ..., Z_p(t))$ is

$$h[t \mid Z_1(t), ..., Z_p(t)] = h_0(t) \exp[\beta_1 Z_1(t) + ... + \beta_p Z_p(t)].$$

Here the β's are called *risk coefficients* and $h_0(t)$ is the arbitrary *baseline hazard rate.* Estimation of the risk coefficients for this model is based on a *partial likelihood function.* While there are several formulations for this partial likelihood we shall use the default partial likelihood available in SAS$^@$, namely *Breslow's* partial likelihood. (See Klein and Moeschberger Section 8.3).

Estimates of the β's, denoted by $b_1,...,b_p$, and the covariance matrix of the estimates are available in the SAS$^@$ procedure PHREG.

When all the factors are fixed then the *relative risk* of the event for a patient with a set of covariates, $Z_1, ...,Z_p$ as compared to a patient with covariates $Z_1^*, ...,Z_p^*$ is the ratio of their respected hazard rates, which in this model is given by

$$\exp[\beta_1 (Z_1-Z_1^*) +...+\beta_p (Z_p-Z_p^*)]. \tag{1}$$

When Z_k are binary covariates (i.e. 0 1 valued) the quantity $\exp[\beta_k]$ is often called the relative risk of the covariate Z_k. Here this quantity is the ratio of the hazard rate of someone with a value of 1 for this covariate as compared to someone with a value of zero for this covariate, when all other covariates are the same for the two individuals. When Z_k is one of the covariates that make up a factor then this is the relative risk of an individual with category Z_k compared to a baseline individual, again all other factors held the same. Relative risk of an individual with category k as compared to an individual with category j of a given factor is given by $\exp[\beta_k-\beta_j]$, which is a special case of (1).

$100x(1-\alpha)$ confidence intervals for the relative risk are given by the following formula:

Estimate $= \exp[b_k]$
Confidence Interval $= (\exp\{b_k- z_{1-\alpha/2} SE[b_k]\}, \exp\{b_k+ z_{1-\alpha/2} SE[b_k]\})$

Estimate $= \exp[\beta_1 (Z_1 - Z_1^*) + ... + \beta_p (Z_p - Z_p^*)]$

Confidence Interval =

$(\exp\{b_1 (Z_1 - Z_1^*) + ... + b_p (Z_p - Z_p^*) - z_{1-\alpha/2} S\}, \exp\{b_1 (Z_1 - Z_1^*) + ... + b_p (Z_p - Z_p^*) - z_{1-\alpha/2} S\}),$

where

$$S^2 = \sum_{j=1}^{p} Var[b_j](Z_j - Z_j^*)^2 + \sum_{i \neq j} Cov[b_j, b_i](Z_j - Z_j^*)(Z_i - Z_i^*)$$

and $Z_{1-\alpha/2}$ is the $(1-\alpha/2)$ percentile of a standard normal.

B. Creating Factors For Dependent Variables

1. Categorical Data

If the variable has k categories then k-1 binary covariates are created. Each covariate is the indicator of whether a patient is in a particular category. One category is the baseline and when a patient is in this category all of the k-1 covariates are zero.

Each category must contain at least 5% of the sample and at least 5% of the events to be considered as a separate category. If this criterion is not met then the category must be collapsed with another biologically compatible category or cases with this category should be excluded from the study.

2. Missing values

When the number of missing values is small or the number of events with missing data is small then these cases are excluded from the study. By a small number of cases we mean less than 5% of the data or less than 20, which ever number is smaller. By a small number of events we mean less than 5% of the events or 5 events, which ever is smaller.

When the number of missing values is large then missing is considered as a separate factor and the number of categories is increased by 1.

These determinations should be made before any attempt at modeling the factors related to the event time is performed and before any diagnostic checks are made.

3. Discretizing a continuous covariate

Categorical covariates are easier to interpret and should be used in most cases. To determine the cut points to use the following procedure is used.

Step 1. Use biologically relevant cut points. These cut points are based on the physician investigators knowledge of the biology of the disease and transplant regime under study. They may be based on the transplant literature, consensus of the Writing or Working committee, or based on accepted practice in previous IBMTR/ABMTR studies. These cut points should be listed and discussed in the study protocol. Some categories for common covariates for all disease are listed in the following table:

Factor	Categories
Karnofsky Score Pre Transplant	<90, ≥90
Patient Age	By Decade (0-9, 10-19,...,40-50,>50)
Donor Age	By Decade (0-9, 10-19,...,40-50,>50)
Year of Transplant	80-85, 86-90, >90
WBC count at Diagnosis	< vrs ≥ 75 x10^9/L

Some disease specific factorsspecific to studies of lukemia are as follows:

Time to achieve first remission	< vrs ≥ 8 weeks
Duration of first remission	< vrs ≥ 8 weeks
Interval between transplant and most recent remission	< vrs > 1 year
WBC at Diagnosis	AML: < vrs ≥ 75 x10^9/L ALL (adults): < vrs ≥ 30 x10^9/L ALL (Children): < vrs ≥ 100 x10^9/L CML : < vrs ≥ 20 x10^9/L

Step 2. When cut points can not be agreed to in step one then a statistical method is used to find the cut point. A set of possible cut points is made. In theory the cut point to discretize a continuous covariate can at any value in the data set that corresponds to an event, the set of cut points will be restricted to "nice" values, typically integers or some multiple of the integers (e.g.. for ages 5, 10,15, 20, etc. years). Separate proportional hazards models are fit which includes only the single factor for each plausible discretation of the covariate. The partial log likelihood is recorded for each of these models (or the -2xlog likelihood value). The categorization which gives the largest of these partial likelihoods is then used in subsequent analyses. Note that in this technique the number of categories must be predetermined and each of the likelihoods is for a factor with the same degrees of freedom.

NOTE: The proposed categories for all continuous covariates must be circulated to the Writing Committee for review before any multivariate analysis is performed.

3. Creating Time Dependent Covariates

There are two types of time dependent covariates, internal and external covariates. Internal covariates are intrinsic to the transplant process (e.g. acute GVHD) and external covariates are artificially created covariates typically arising by the need to either check the proportionality assumption or to adjust fixed covariates for non-proportional hazards. The creation of external covariates is discussed in Section V.C.

An internal covariate for an intermediate event is coded as follows:

$$Z(t)= \begin{cases} 1 \text{ if time to intermediate event} \leq t \\ 0 \text{ otherwise} \end{cases}$$

In PROC PHREG we could code acute GVHD as follows:

```
PROC PHREG;
MODEL TSUR*DEAD(0)=AGVH;
IF TAGVH <=TSUR AND IAGVH=1 THEN AGVH=1; ELSE AGVH=0;
```

Here TSUR is the time to the event; DEAD the event indicator with 0 indicating a censored observation; TAGVH the time to acute GVHD and IAGVH the indicator of acute GVHD with 1 denoting that acute GVHD has occurred.

Caveat emporia: When a time dependent covariate for an intermediate event is used only patients at risk for the event should be in the data set. For example to study acute GVHD only patients who have survived at least 21 days are included in the study. See Section III for these inclusion criterion.

C. Checking Model Assumptions

1. Testing for proportional hazards

To check the assumption of proportional hazards an external time dependent covariate approach is used. Here a time dependent covariate is created for each of the covariates which make up a given factor. The covariate is of the form $Z(t) = Z \ln(t)$. A model is fit with both the orginal fixed time covariates and the created time dependent covariates. If the factor has k degrees of freedom then a Wald test, with k degrees of freedom, is performed to test that the hypotheses all the risk coefficients associated with the time dependent covariates are equal to zero. If this hypothesis is rejected than the factor has non proportional hazards. A 5% signficance level is used for this test.

The testing for proportional hazards is performed separately for each factor. When the goal of the analysis is to test a particular hypothesis then the main factor of interest is included in each model.

The SAS@ code to perform this analyses for a 3 degree of freedom factor with covariates Z1, Z2, Z3, a time to event TSUR and and event indicator DEAD (with code 0 for censored observations) is as follows:

```
PROC PHREG;
MODEL TSUR*DEAD(0)=Z1 Z2 Z3 ZP1 ZP2 ZP3;
PROP: TEST ZP1=ZP2=ZP3=0;
ZP1=Z1*LOG(TSUR);
ZP2=Z2*LOG(TSUR);
ZP3=Z3*LOG(TSUR);
```

B ADJUSTMENTS FOR NON PROPORTIONAL HAZARDS

When the proportional hazards assumption is rejected than an adjustment to the model is needed. The adjustment depends on the number of non proportional hazards found, and whether estimates or tests of the effect of the factor with non proportional hazards is of interest.

If there are few factors, the factors are not of primary interest in the study and these factors have few categories then the analyses should be based on a stratified model. Here a single variable is created which includes a distinct value (the actual values of the variable are irrelevant) for each level of the factor. The model is then stratified on these new variables. In the above example the following SAS@ code would be used to test a hypotheses about a new covariate, MAIN, stratifying on the factor Z1, Z2, Z3.

```
DATA NEW; SET OLD;
STRAT=0;
IF Z1=1 THEN ST=1;
IF Z2=2 THEN ST=2;
IF Z3=3 THEN ST=3;
PROC PHREG;
MODEL TSUR*DEAD(0)=MAIN;
STRATA ST;
```

A rule of thumb for determining if stratification is to be used is that each stratum should contain at least 20 observations and at least 5 events.

When stratification is not warranted then an artificial time dependent covariate is created to handle the non proportional hazards. That is we create two time dependent covariates for a given non-proportional hazards covariate. These are the early ($t \leq \tau$) and late ($t > \tau$) effects of covariate represented by the covariates

$$ZE(t) = \begin{matrix} Z \text{ if } t \leq \tau \\ 0 \text{ otherwise} \end{matrix} \qquad ZL(t) = \begin{matrix} Z \text{ if } t > \tau \\ 0 \text{ otherwise} \end{matrix}.$$

To find τ the approach for finding the best cut point for a continuous covariate is used (See Section V.B.3.). In theory the only values one needs to check are the observed event times but in practice one should attempt to pick a set of biologically plausible values τ and check the likelihood at these points. Once τ is found then the proportional hazards assumption must be checked for each of the newly created time dependent covariates. If the assumption is found not to be valid then the above process is repeated.

D. Stepwise Model Building

1 Initial Search

Stepwise model building is done either in hypothesis testing or exploratory analysis problems. The difference between the two is in the hypothesis testing situation the main effect to be tested is included in all models. The procedure is only used after the factors have been checked for proportional hazards and all problems with missing values have been resolved by either cleaning the data set or by creation of a missing category. The data set for this procedure must be the same for each of the models to be run for the procedure to be valid. The automated procedures in SAS[@] can only be used when all factors are single degree of freedom factors.

If there are M factors (other than the main effect) to be considered then the model building is as follows:

Step 1: Fit M models with each model containing only a single factor. Find the Wald p-value associated with the test of no effect of this factor on outcome. The factor with the smallest p-value (<0.05) is put into the model. Note if none of the factors are signficant at the 5% level then the final model has no factors in it (except for the main effect in the hypothesis testing framework).

Step J, J=2,...,M:

A. Fit M-(J-1) models with the J-1 factors left in the model from step J-1 along with one of the M-J+1 factors not in the model at the previous step included in the model. Find the Wald p-value for each new factor.

B. If none of the new factors are signficant at the 5% level (i.e. all have a p-value >0.05) then stop and used the model from step J-1.

C. If one of the factors has a p-value less than 0.05 then add it to the model and got to step J+1.

The model from this procedure is the working model. If all factors (except the possible main effect) are significant then it is the stage one model. If there is some factor, added at an earlier step, which is no longer significant then further tests should be performed on the model to remove non significant factors. In most cases this means that two of the factors are highly associated and the covariate which is simplest to interpret should be included in the final model. Finding the final model in this case will involve comparing models with and without the factor. Note models can be compared on the basis of the Akaike Information Criterion, $AIC = -2 \log L + 2p$, where p is the number of regression parameters in the model and L is the partial log likelihood.

2. Collapsing Categories

Once a first stage model is found it is reasonable to examine, in this model, the potential of collapsing categories for the individual factors. This should be done in collaboration with the physician investigator on the project so that biologically implausible categories are not created. If there are k categories there are $kx(k-1)/2$ tests to be performed. The tests are comparisons of each category with each other. For example if there are four categories, coded by three binary covariates Z1, Z2, and Z3, then the $4x3/2=6$ tests are as follows:

H_0 $\beta 1 = 1$ (category 1 = baseline)

H_0 $\beta 2 = 1$ (category 2 = baseline)

H_0 $\beta 3 = 1$ (category 3 = baseline)

H_0 $\beta 1 = \beta 2$ (category 1 = category 2)

H_0 $\beta 1 = \beta 3$ (category 1 = category 3)

H_0 $\beta 2 = \beta 3$ (category 2 = category 3).

Based on these tests the decision to recategorize the factor can be made and a phase two model with revised factors can be constructed. Of course the factors need to be retested in this revised model.

3. Testing for interactions

Interactions are tested in the phase two model. Which interactions to check should be a collaborative decision between the physician investigator and the statistician. In general it is advisable to check for interactions between a main effect and each of the factors being used to adjust for differences in the treatment arms.

To check for an interaction of a factor with M levels and a factor with P levels requires the creation of $MxP-1$ binary covariates. To test for interaction we create $(M-1)x(P-1)$ new covariates by multiplying each of the $(M-1)$ binary covariates of factor 1 by one of the $(P-1)$ covariates of factor 2. A model is fit with the main effects of factors 1 and 2 ($M+P-2$ covariates) and the $(M-1)x(P-1)$ new covariates (and any other factors in the phase two model). A Wald test, with $(M-1)x(P-1)$ is performed to test the hypothesis that the interaction covariates are all zero. If this test has a p-value greater than 0.05 the an interaction is not present.

If an interaction is found between two factors then the two factors are pooled into a single factor with (MxP) categories ($MxP-1$ binary covariates) found by picking one category from factor 1 and one from factor 2. Using the technique in Section V.D.2 the dimensionally of this factor is reduced to achieve a new model.

E Testing for center effects

To test for possible center effects a random effects score test developed by Commange and Andersen (1995) is used (See Klein and Moeschberger Section 13.2). The test is performed on the final model for the study and tests the hypothesis that there is no center effect against the hypothesis of a random center effect. A FORTRAN program is available to perform the test. Input to the program is the estimates of the risk coefficients from the final model, the estimated covariance matrix of the risk coefficients and the raw data.

If the score test rejects the hypothesis of no center effect then an adjustment for this effect is made using a Gamma frailty model (See Klein and Moeschberger Section 13.2). A SAS macro for this procedure is available.

F PROC PHREG

The SAS procedure PHREG is used to perform most of the analyses discussed in this Section. It can be used with a slight modification for either right censored data or for right censored and left truncated data. The general form of the procedure for right censored data is

PROC PHREG options;
MODEL time*censoring(codes) = list of covariate/ options;
STRATA list /option;
Label : TEST hypothesis; (Can be repeated)
Program Statements.;
Here the code in italics is optional while the code in Caps is required. In this case time is the name of the variable containing the on study times, censoring is the name of the variable containing the censoring codes and values in (code) is a list of the codes for <u>censored</u> observation.

For left censored or delayed entry data an alternate form of the model statement is used. Here we say
MODEL (time1,time2)*censoring(codes) =list of covariate/ options;
In this case time1 is the time the subject first becomes at risk and time2 is the time at which the person was last seen. Individuals are in the risk set only for times between time1 and time2.

Before discussing the options for the procedure consider the following two examples of the model statement. For the first suppose that only transplant patients are being analyzed, that the event is overall survival with an on study time of intxsurv and an event indicator of survhi with values of 1 and 3 corresponding to censored observations. Then the model statement is coded as
MODEL intxsurv*survhi(1,3) = list/options;
If we wished to compare transplant to chemotherapy patients, say, then the second form of the model would be used. Suppose the time on study is measured from diagnosis and the variable TSUR holds the time values and the death indicator is DEAD with a value 0 corresponding to a censored observation. BMT patients are left truncated in this model and only become at risk at the time of transplant, while chemotherapy patients are at risk at time 0. We create a time variable ETIME, with value 0 for a chemotherapy patient and a value equal to the waiting time from diagnosis to transplant for a BMT patient. The model statement is now
MODEL (ETIME, TSUR)*DEAD(0) = list of covariate/ options;
Options of primary interest in the PHREG procedure are as follows.
In the PROC statement :
SIMPLE -- Gives the summary statistics for each fixed covariate.
COVOUT OUTEST=data set --Outputs a SAS data set with the parameter estimates and the covariance matrix. This can be inputed into PROC IML to find, for example, relative risks not routinely computed in PHREG.
In the MODEL statement
COVB -0 Prints the covariance matrix of the estimates
RISKLIMITS-- Prints estimates and 95% confidence intervals for the relative risk of each covariate compared to baseline.

ITPRINT--Prints the iteration history. This is important to look at to determine if the numerical routine to estimate the risk coefficients has in fact converged. NOTE SAS will not routinely tell you that there is a problem with convergence.

In the STRATA statement

MISSING -- Tells SAS to have missing as one of the strata. If this is not there SAS will toss out anyone with a missing value for any of the strata.

VI. Modeling 100 Day Mortality

Special techniques are needed to model 100 day mortality (or mortality at any fixed point in time). The techniques in section V are not appropriate since they model the entire survival curve, not the value at a fixed point in time. The approach used to develop a multivariate model parallels that discussed in Section V using a logistic regression model rather than a proportional hazards model.

To model 100 day mortality the data set consists of all individuals who die in the first 100 days and all patients who survive with at least 100 days of follow-up. Any patient with less than 100 days of follow-up who did not die is removed from the data set.

The only covariates that can be modeled are those known at the time of transplant. No time dependent covariates are allowed. Factors are created as discussed in Section V and missing values are handled as discussed there. A single dependent variable is created with a value of 1 if the patient dies in the first 100 days and a value of 0 if they survive 100 days.

The statistical model for the data is the logistic model, namely,

$$\ln\left\{\frac{P[100 \text{ day survival} \mid Z_1, ...,Z_p]}{1-P[100 \text{ day survival} \mid Z_1, ...,Z_p]}\right\} = \beta_1 Z_1 + ...+\beta_p Z_p.$$

In place of the relative risk, the odds ratio is used for 100 day mortality. Here $\exp[\beta_1]$, for example, is the ratio of the odds for an individual with covariate $Z_1 =1$ as compared to the odds for an individual with $Z_1=0$ (and all other covariates the same). More complicated odds ratios can be computed using the formulas in Section V with the relative risk replaced by odds ratio.

Model building for 100 day mortality is identical to that for the Cox model. The exception is that PROC LOGISTIC is used in place of PROC PHREG. The format for the procedure is:

PROC LOGISTIC options;
MODEL Y=list/options;
Label: TEST hypothesis;

Here Y is the indicator of survival at 100 days. Options are identical to those in PROC PHREG.

VII. WRITING COMMITTEE MEMOS

The primary mission of the IBMTR and ABMTR is to bring together data and expertise from many transplant centers to facilitate scientific studies of important issues in hematopoietic stem cell transplantation. IBMTR/ABMTR studies benefit not only from the large numbers of patients available for analysis but, just as importantly, from the diverse talents of participants in the Working/Writing Committees which supervise each study. To derive maximum benefit from this expertise requires good communication between the Statistical Center and the Committees and among Committee members. Face-to-face meetings are infrequent, since members are geographically widely dispersed. The Writing Committee Memo is the primary vehicle for this communication. Writing Committee memos should provide concise information about the status of studies at each stage of progress, allowing Writing Committee members to provide substantive input on all aspects of the study including design, patient population, explanatory and outcome variables, and interpretation of univariate and multivariate analyses. The following is a list of landmarks in a study's course which generally warrant preparation and distribution of a Writing Committee memo. It should not be considered all-inclusive. Writing Committee memos should be prepared whenever substantive deviations from the original study plan are felt to be necessary and/or whenever the Committee's formal input would be beneficial.

(1) Study proposal

The original study proposal submitted for consideration approved should be circulated to the relevant Working Committee(s) once the study is approved, soliciting individuals interested in participating in the Writing Committee. The cover letter for this memo should briefly restate the primary objectives of the study, the intended study population and the initial sample size calculations made when the proposal was considered. The principle investigator should be identified with contact information (address, phone, fax, e-mail). Centers contributing data for large numbers of patients meeting the provisional patient eligibility criteria should be determined. If these centers do not have a representative on the relevant Working Committee(s) for the study, the center director should also receive this memo offering the opportunity to participate on the Writing Committee. This memo should also request suggestions for study design. Example: "The Statistical Center will shortly prepare a protocol (analysis plan) for _____ in collaboration with the (principle investigator). If you have suggestions related to the study design, including patients and outcomes to be studied and variables to be considered, please send these in writing to the (principle investigator) with a copy to the Statistical Center." The memo should include a fax response sheet asking the respondent to indicate whether or not he/she wishes to be part of the Writing Committee and having space for comments.

(2) Study Protocol (See section I)

The Study Protocol should be prepared and reviewed by the principle investigator and then distributed to the Writing Committee, asking for comments. If the comments result in substantive revisions to the protocol, a revised draft should also be circulated.

(3) Description of the study population

The patient eligibility criteria should be clearly defined and patient-, disease-, and treatment-related variables described. Overall outcomes may be included but no univariate or multivariate analyses. Categories of variables for these analyses should be defined.

(4) Univariate analyses/Multivariate analyses

Results should be presented clearly in Table and Figure format with results summarized in the cover letter. Any surprising findings should be highlighted in the cover letter.

(6) Revised analyses

Additional analyses may be performed or other changes to the study done in response to comments from Writing Committee members. These should be presented in table format, with a cover memo addressing each of the comments/criticisms received. It is important that Committee members are notified in writing that their suggestions were taken seriously (as they are) and appropriate action taken.

(7) Manuscript drafts

There will be at least two drafts circulated (often more), the first draft and the draft to be submitted for publication. The latter should include Authorship and Assignment of Copyright forms for signature, if required by the journal to which the paper will be submitted.

(8) Confidentiality

Unpublished data in Writing Committee memos are confidential. Each Writing Committee memo should include the following statement:

"The enclosed data are confidential. If used publicly, the following statement must be included: 'The data presented here were obtained from the IBMTR/ABMTR Statistical Center. The analysis has not been reviewed or approved by the Advisory Committee of the IBMTR or ABMTR. The data may not be published without prior approval of the Advisory Committees.' If the data are used in an oral presentation, please send us the name, place and dates of the meeting where the data are presented, and the title of your presentation."

(9) Authorship

Membership on a Writing Committee is not sufficient for authorship on a manuscript. Each Writing Committee memo should include the following statement:

"You should note that IBMTR/ABMTR rules require that any member of a Writing Committee who does not make a substantive contribution to the design, analysis, interpretation or manuscript withdraw as a co-author or, alternatively, the lead author may remove names of non-contributors."
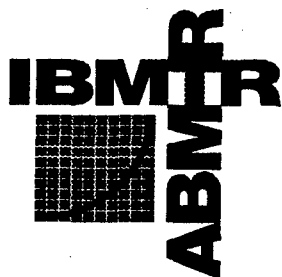
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Appendix A   IBMTR/ABMTR Study Proposal Form

Statistical Center
Medical College of Wisconsin
8701 Watertown Plank Road
Milwaukee, WI, 53226, USA
Telephone: 414-456-8325
Fax: 414-266-8471
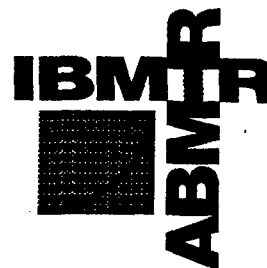
IBMTR
ABMTR

STUDY PROPOSAL GUIDELINES

The rules of the IBMTR/ABMTR state that anyone may propose a study. The person proposing the study must complete a Study Proposal Outline. This is reviewed by the Statistical Center and relevant Working Committee Chair(s). Studies deemed feasible and consistent with the Registries' scientific goals are forwarded to the Working Committee for further input and assignment of a priority score. Studies are initiated at the discretion of the Working Committee Chair, Scientific Director and the Advisory Committee Chair based on priority scores, competing projects and available resources. A Writing Committee is formed to supervise the study. Interested members of the Working Committee and others are permitted to serve on the Writing Committee. To assure co-authorship of the manuscript, members of the Writing Committee must make timely and substantive contributions to study design, data analysis, interpretation of results or preparation of the typescript for publication. Members of the Writing Committee who do not fulfill this requirement are expected to withdraw as a co-author or, alternatively, their names will be deleted by the lead author.

Lead authorship (the person with primary responsibility for the study) is usually the person first proposing a study. The only exception to this policy is, for example, if the person proposing a study has only a trivial proportion of the cases to be studied, while a member of the Working Committee with a large proportion of the patients also requests primary responsibility. When multiple requests for primary responsibility for a single study are received, the person with the largest number of patients in the study is awarded primary responsibility.

The person awarded primary responsibility is required to prepare a first draft of the typescript within 60 days of first receipt of data from the Statistical Center. Failure to do so can result in forfeiture of lead authorship.

MMH:d
Enclosure
F:\IBMTR-U\D\DATA_DETTA\NEW-STUD\@STUDYFR.LTR

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IBMTR
ABMTR

[Name of Study]

STUDY PROPOSAL OUTLINE

Please prepare a brief description (no more than three pages) of the proposed study as you envision it. Use the outline below and send your description to the Statistical Center as soon as possible.

I. Study Title

II. Specific Aims

III. Scientific Justification
(1-2 paragraphs on the key issues and their importance)

IV. Patient Eligibility Criteria

V. Design of Study (Scientific Plan)
This section should describe how the specific aims will be addressed using information from the IBMTR/ABMTR database. Carefully review IBMTR/ABMTR data collection forms to determine data availability. Include a list of variables you believe will be informative and the outcome variables you wish to analyze. Specify whether additional data would have to be collected and how this would be done.
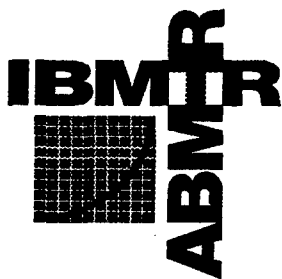
IBMTR/ABMTR Statisticians' Manual

Appendix B   Sample IBMTR/ABMTR Study Protocol

UNRELATED DONOR VERSUS AUTOLOGOUS BONE MARROW TRANSPLANTS FOR ACUTE MYELOGENOUS LEUKEMIA

(NOVEMBER 1996)

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Table of Contents

1.0   OBJECTIVES

To compare outcome of unrelated donor and autologous bone marrow transplants for acute myelogenous leukemia (AML) in first and second remission. Outcomes to be studied include:

1.1   Hematopoietic recovery;
1.2   Treatment-related mortality;
1.3   Leukemia recurrence;
1.4   Leukemia-free survival;
1.5   Overall survival.

2.0   BACKGROUND

Intensive induction and consolidation chemotherapy has improved the outcome of patients with AML. About 60% of adults and 80% of children achieve complete remission. However, leukemia recurs in 50-70% (1-11). Post-consolidation myeloablative treatment and bone marrow transplantation from an HLA-identical sibling is associated with lower recurrence rates and 50-60% five-year disease-free survival rates for patients transplanted in first remission (12-14). Autologous or unrelated donor transplants are of interest as alternative treatment options, since only 30% of patients have an HLA-identical sibling.

2.1   AUTOLOGOUS TRANSPLANTATION

Treatment-related mortality after autotransplants is about 15% compared to 30% after HLA-identical sibling transplants. Three-year probabilities of survival after autotransplants for AML are 35-60% for patients treated in first remission and 25-35% for patients in second remission (15-22). Relapse rates are higher after autologous transplants compared to HLA-identical sibling transplants. This may be a result of leukemic contamination of the graft and/or lack of graft-versus-leukemia effects. Some data suggest less relapse and better outcome with total body irradiation (TBI) containing regimens (21) and ex vivo purging with mafosfamide (15, 23), 4-hydroxycyclophosphamide (24-26) or monoclonal antibodies (27). Regardless of transplant regimen, relapse (30-50% incidence for patients transplanted in first remission and 40-60% for those transplanted in second remission) is the major cause of treatment failure (18, 20, 22).

2.2   UNRELATED DONOR TRANSPLANTATION

Until recently, use of unrelated donors for transplants was severely limited by availability. Availability increased dramatically over the past five years through establishment of large panels of HLA-typed volunteer donors, such as that maintained by the National Marrow Donor Program (NMDP). Approximately 70% of patients searching the NMDP file find an HLA-A, B and DR antigen matched donor on preliminary searches though fewer actually proceed to

transplant. It takes 2-6 months before a suitable donor is identified, evaluated and scheduled for donation. Many patients will relapse in this interval. The few studies that report unrelated donor transplants show lower leukemia-free survival than after HLA-identical sibling transplants. Poorer outcome is attributable to higher treatment-related mortality from graft-versus-host disease (GVHD). The risk of relapse is low, probably due to GVHD-associated graft-versus-leukemia effects (28, 29). In one study from UCLA, matched unrelated donor transplants for high risk AML had two-year leukemia-free survival rates of 23±12%, one-year relapse rates of 24±16% and 57% grade II-IV GVHD (30). The Canadian Bone Marrow Transplant group reported 40% two-year event-free survival after matched unrelated donor transplants for various malignancies (7/35 were AML); most transplants are done in relapse or second or subsequent remission (31). The NMDP recently reported results of 79 AML patients receiving unrelated donor transplants (32). Twenty-five patients, transplanted in first and second remission, had two-year disease-free survival of 40%. Forty percent leukemia-free survival at two years was reported in the low-risk group and 20% in the high-risk group (32). The probability of grade II-IV acute GVHD was 64% and of chronic GVHD 55% (33). This result was consistent with an NMDP report of 462 patients with various malignancies receiving unrelated donor transplants (33). T-cell depletion of donor marrow reduces the incidence of GVHD (25-50%) after unrelated donor transplants (34-37) but does not convincingly increase survival. The Seattle group compared outcome for unrelated donor and autologous transplants in advanced acute leukemia (n=120) (38). There was not a significant difference (p=0.45) in five-year leukemia-free survival. However, only six of 23 unrelated and 11 of 41 autologous transplant recipients with AML were transplanted in second remission and none in first remission.

3.0 PRELIMINARY STUDIES

The Autologous Blood and Marrow Transplant Registry of North America (ABMTR) has collected data on 469 recipients of autotransplants for AML in first or second remission, registered between January 1, 1989 and December 31, 1994. Characteristics of these patients are shown in Table 1.

The NMDP facilitated 163 unrelated donor transplants for AML in first or second remission in the United States during the same period. Characteristics are shown in Table 2.

The International Bone Marrow Transplant Registry (IBMTR) has collected data for 55 unrelated donor transplants for AML in first and second remission, transplanted during the same period in non-USA centers. Characteristics are shown in Table 3.

4

4.0   ANALYSIS PLAN

4.1   ELIGIBILITY CRITERIA

The analysis will include persons receiving autologous or unrelated donor bone marrow transplants for AML in first and second remission between January 1989 and December 1994, with age ≤ 50 years, reported to the ABMTR, IBMTR or NMDP.

4.2   DEFINITION OF ENDPOINTS

The following endpoints will be studied:

4.2.1   Hematopoietic recovery: Time to neutrophils (ANC) > 0.5 x10^9/L for three consecutive days will be the primary measure for comparisons of hematopoietic recovery.

4.2.2   Leukemia recurrence: Time to first leukemia recurrence will be compared. Patients will be censored at death in continuous complete remission, second transplant or, for patients surviving in continuous complete remission, at last contact.

4.2.3   Leukemia-free survival: Leukemia-free survival is defined as survival in continuous complete remission. Leukemia relapse and death in remission are considered events. Patients surviving in continuous complete remission will be censored at last contact.

4.2.4   Survival: Events are deaths from any cause. Surviving patients are censored at last contact, regardless of intervening treatment.

4.3   POTENTIAL CONFOUNDING VARIABLES

Many factors may affect transplant outcome. Since this is a non-randomized study, careful attention will be paid to potential confounding factors. These are outlined below with suggested categories for analysis.

4.3.1   Patient-related factors
   - Age: continuous
   - Gender: male vs female
   - Karnofsky performance score: < vs ≥ 90%

4.3.2   Disease related factors
   - Remission status: first remission (CR1) vs second remission (CR2)
   - Cytogenetic abnormalities: t(9;22), -7, -7q, -5, -5q, 11q (±others) vs others vs none vs not tested/available
   - FAB classification: FAB M1, 2 vs M3 vs M4 vs M5-7 vs unclassified

5

- WBC count at diagnosis: $<$ vs $\geq 75 \times 10^9/L$
- Prior treatment: Use of high-dose cytarabine ($\geq 1 g/m^2/d$) during induction/consolidation chemotherapy: yes vs no
Time to achieve first remission: $<$ vs ≥ 8 weeks
Duration of first remission: $<$ vs ≥ 1 year

4.3.3 Transplant-related factors (allo and auto)
- Year of transplant: continuous variable
- Interval between transplant and most recent remission: continuous variable
- Conditioning regimen: TBI-based vs other possible categories
- Growth factors post-transplant: none vs G-CSF/GM-CSF (started within 72 hours posttransplant)

4.3.4 Transplant-related factors (autologous)
- Marrow purging: yes vs no

4.3.5 Transplant-related factors (allogeneic only)
- GVHD prophylaxis: CsA vs MTX vs CsA+MTX vs T-cell depletion
- Gender-match: male-female vs female-male vs gender-match
- Donor age: continuous
- CMV status donor/recipient: -/- vs -/+ vs +/+ vs +/-
- Donor recipient HLA-match: definition to be determined

4.3.6 Time varying effects

Experience has shown that some of the factors listed in 4.3.1 - 4.3.5 have differential effects on outcome in different time periods. In particular, the primary factor of type of transplant most likely will have different effects in the early and late periods after transplant. This problem is addressed by considering models that allow for distinct relative risks in different time periods.

4.4   DATA RETRIEVAL

The IBMTR/ABMTR statistical center and NMDP will each prepare a data file for patients meeting the eligibility criteria in section 4.1 and including the following variables:

4.4.1   Patient-related variables
- Patient ID number
- Date of birth
- Gender
- Karnofsky performance score pretransplant
- CMV status pretransplant
- Recipient HLA-type (for patients who received an unrelated donor graft)

4.4.2   Disease-related variables
- Date of diagnosis
- Cytogenetics
- FAB classification
- WBC count at diagnosis
- High-dose cytarabine treatment
- Number of induction courses to CR1
- Number of consolidation courses in CR1
- Date of CR1
- Date of first relapse (for CR2 patients)
- Date of CR2 (for CR2 patients)
- Remission state at transplant

4.4.3   Transplant-related variables (allo and auto)
- Date of transplant
- Conditioning regimen
- Center ID number

4.4.4   Transplant-related variables (autologous)
- Bone marrow purging

4.4.5   Transplant-related variables (allogeneic)
- GVHD prophylaxis
- T-cell depletion
- Donor date of birth
- Donor gender
- Donor CMV status
- Donor HLA-type

4.4.6 Follow-up parameters
- Date of achievement of ANC >0.5 x10⁹/L as defined in section 4.1.1
- Date of onset acute and chronic GVHD (unrelated only)
- Highest grade of acute and chronic GVHD (unrelated only)
- Date of first posttransplant leukemia recurrence
- Date of death
- Cause of death
- Date of second transplant, if applicable
- Date of last contact

4.5   STATISTICAL METHODS

Patient-, disease- and transplant-related factors will be compared between the two
transplant types, using Chi-square test for categorical and Mann-Whitney test for
continuous variables.

The data will be analyzed by using a proportional hazards model (39). For this
analysis separate models will be fit, using relevant risk factors (section 4.3), to
both the autologous and unrelated donor groups. These models will identify
variables that require adjustment in each patient group to assure that the
comparisons made in later stages are not confounded by other factors. For both of
these models the proportional hazards assumption for all variables will be
examined using a time-varying covariate and by graphical methods. Factors found
to have non-proportional hazards will be adjusted for in subsequent analysis by
using a stratified proportional hazards model or by using a set of time-dependent
covariates.

Once a set of factors associated with outcome is determined for each of the
transplant types, models which directly compare the two types of transplants will
be built. A step in this process is to determine if the effect of a given factor is the
same for both types of transplants. This will be examined by fitting a proportional
hazards model, stratified on transplant type, and examining the interaction term
between the factor of interest and the type of transplant. If this interaction term is
significant then the final model will have an interaction term between the factor and
type of transplant and separate inferences about the effect of transplant type will be
made for each level of the confounding factor. The final model constructed by this
technique will include all the factors found plus a term for transplant type. The
proportional hazards assumption will again be examined, and should it be found
that the hazards are non-proportional for the effects of interest, the best fitting
model with time-varying risk coefficients will be found. Here the best cut-off point
between early and late effects is found by finding the model that yields the largest
partial likelihood.

Multivariate regression using partial logistic regression will also be used to
compare outcome of autologous and unrelated donor transplants, controlling for

the risk factors identified above (40). Unlike traditional logistic regression, this technique allows for censored data much like a Kaplan-Meier curve or Cox proportional hazards model. The partial logistic model can be very restrictive, imposing conditions analogous to the Cox model, or it can be very flexible, approaching the non-parametric Kaplan-Meier curve as the number of parameters modelled increases. The number of parameters needed will be determined by the fit to the data. A parametric bootstrap will be used to compute confidence intervals and perform tests of significance (41, 42).

4.6 SAMPLE SIZE CALCULATIONS

Table 1 describes 469 patients receiving autotransplants for AML in first and second remission transplanted between January 1989 through December 1994 for whom comprehensive data are available. Three hundred thirty six patients were transplanted in CR1 and 133 in CR2. Table 2 describes the 163 unrelated donor transplants reported to the NMDP in the same period. Sixty one transplants were for AML in CR1 and 102 for AML in CR2. Table 3 describes the 55 non-USA unrelated donor transplants reported to the IBMTR in the same period. Twenty four transplants were for AML in CR1 and 31 for AML in CR2.

Tables 4 and 5 show the power to detect specified differences in leukemia-free survival with autologous versus unrelated donor transplants, assuming inclusion of all unrelated donor transplants reported to either NMDP or IBMTR (Tables 2 and 3). The displayed data are based on the assumption that 50% of autotransplant recipients for AML in CR1 and 30% of those with AML in CR2 are alive and disease-free three years post-transplant (non-published data from ABMTR). It must be noted that the probability of detecting a difference between treatment groups with given power depends on the amount of censoring and variation in risk factors between the groups. This may induce potential discrepancies that interfere with the power calculations.

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Table 1. Characteristics of patients with AML in CR1 and CR2, who received autologous bone marrow transplantation and for whom comprehensive data are available.

Variable	CR1 (%)[a] median (range)[b]	CR2 (%)[a] median (range)[b]
Number of patients	336	133
Year of transplant		
1989	45 (13)	25 (19)
1990	50 (15)	28 (21)
1991	81 (24)	22 (17)
1992	73 (22)	29 (22)
1993	80 (24)	26 (20)
1994	7 (2)	3 (2)
Age in years	25 (1-65)	32 (1-63)
Male sex	164 (49)	73 (55)
Karnofsky performance score ≥ 90%	282 (84)	97 (73)
WBC at diagnosis (x10^9/l)	8 (1-690)	7 (1-479)
FAB		
M1	50 (15)	26 (20)
M2	92 (27)	42 (32)
M3	35 (10)	13 (10)
M4	66 (20)	36 (27)
M5	49 (15)	7 (5)
M6	---	---
M7	6 (2)	2 (2)
Unclassified	22 (7)	7 (5)
Granulocytic sarcoma	16 (5)	16 (5)
Conditioning regimen		
BU + CY ± other	236 (70)	93 (70)
TBI + CY ± other	21 (6)	19 (14)
TBI + other	31 (9)	9 (7)
BU ± other	13 (4)	3 (2)
CY + VP16 + nitrosurea	20 (6)	3 (2)
Graft purged	198 (60)	92 (70)
Missing[c]	5 (1)	2 (2)

[a] for categorical variables, [b] for continuous variables, [c] data are only missing for purging
Abbreviations: WBC=white blood count; FAB=French-American-British; BU=busulfan; CY=cyclophosphamide; TBI=total body irradiation

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Table 2. Characteristics of unrelated donor transplants for AML in CR1 and CR2 from the NMDP.

Variable	CR1 (%)[a] median (range)[b]	CR2 (%)[a] median (range)[b]
Number of patients	61	102
Year of transplant		
1989	3 (5)	4 (4)
1990	7 (11)	10 (10)
1991	7 (11)	24 (23)
1992	12 (20)	15 (15)
1993	15 (25)	16 (16)
1994	17 (28)	33 (32)
Age in years	25 (0-48)	26 (0-55)
Male sex	43 (71)	62 (61)
Karnofsky Performance score ≥90%	52 (85)	77 (75)
Conditioning regimen		
Bu + CY	12 (20)	16 (16)
TBI + CY	-	-
TBI + CY + other	32 (53)	58 (57)
TBI + other	3 (5)	7 (7)
TBI + Cy + Arac	9 (15)	12 (12)
TBI + Cy + VP16	5 (8)	9 (9)
GVHD prophylaxis		
CsA	1 (2)	3 (3)
CsA + other, no MTX	2 (3)	9 (9)
CsA + MTX	27 (44)	52 (51)
T-cell depletion	-	-
T-cell depletion + other	25 (41)	28 (27)
Other	6 (10)	10 (10)
Donor male sex	31 (51)	65 (64)
Donor age	35 (20-52)	37 (21-55)

[a] for categorical variables, [b] for continuous variables.
Abbreviations: BU=busulfan; CY=cyclophosphamide; TBI=total body irradiation; CsA=cyclosporin; MTX=methotrexate

Table 3.   Characteristics of unrelated donor transplants for AML in CR1 and CR2 reported to the IBMTR.

Variable	CR1 (%)[a] median (range)[b]	CR2 (%)[a] median (range)[b]
Number of patients	24	31
Year of transplant		
1989	2 (8)	3 (10)
1990	3 (13)	3 (10)
1991	2 (8)	7 (23)
1992	5 (21)	8 (26)
1993	6 (25)	3 (10)
1994	6 (25)	7 (23)
Age in years	20 (1.3-50)	25 (3.6-46)
Male sex	14 (58.3)	16 (51.6)
Karnofsky Performance score ≥90%	17 (70.8)	25 (80.6)
WBC at diagnosis (x10^9/L)	9.6 (1.3-210)	6.3 (0.7-199)
missing	1 (4)	2 (6)
FAB		
M1	5 (21)	5 (16)
M2	3 (13)	8 (26)
M3	-	10 (32)
M4	7 (29)	4 (13)
M5	5 (21)	3 (10)
M6	4 (17)	-
unclassified	-	1 (3)
Conditioning regimen		
Bu + CY	4 (17)	2 (6)
TBI + CY	9 (38)	10 (32)
TBI + CY + other	6 (25)	9 (29)
TBI + other	-	1 (3)
TBI + Cy + Arac	-	2 (6)
TBI + Cy + VP16	4 (17)	5 (16)
Other	1 (4)	2 (6)
GVHD prophylaxis		
CsA	1	3 (10)
CsA + other, no MTX	1	2 (6)
CsA + MTX	17	18 (26)
T-cell depletion	1	1 (3)
T-cell depletion + other	4	7 (23)
Donor male sex	35.9 (0.4-50)	35 (21-56)
Donor age	14 (58.3)	20 (64.5)

[a] for categorical variables, [b] for continuous variables. Abbreviations: BU=busulfan; CY=cyclophosphamide; TBI=total body irradiation; CsA=cyclosporin; MTX=methotrexate

Table 4.   Power to detect a difference in leukemia-free based on 50% 3-year leukemia-free survival in 336 evaluable autologous transplants (H_0) and 85 evaluable unrelated donor transplants (H_a) for AML in first remission.

H_a	Difference in LFS (%)	Power	H_a	Difference in LFS (%)	Power
55	5	0.1290	45	5	0.1290
60	10	0.3845	40	10	0.3845
65	15	0.7127	35	15	0.7127
70	20	0.9258	30	20	0.9258
75	25	0.9912	25	25	0.9912
80	30	0.9996	20	30	0.9996

H_a = assumed LFS in unrelated donor transplants

Table 5.   Power to detect a difference in leukemia-free based on 30% 3-year leukemia-free survival in 133 evaluable autologous transplants (H_0) and 133 evaluable unrelated donor transplants (H_a) for AML in second remission.

H_a	Difference in LFS (%)	Power	H_a	Difference in LFS (%)	Power
35	5	0.1377	25	5	0.1474
40	10	0.4015	20	10	0.4714
45	15	0.7171	15	15	0.8418
50	20	0.9177	10	20	0.9874
55	25	0.9863	5	25	0.9999
60	30	0.9988			

H_a = assumed LFS in unrelated donor transplants
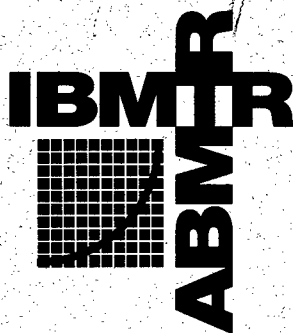
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Autologous Blood & Marrow Transplant
ABMTR Newsletter

December 1998   **Volume 5, Number 1**

REGISTER NOW...
1999 Tandem BMT Meetings at Keystone Resort, Colorado

by D'Etta Waldoch, CMP, IBMTR/ABMTR Associate Director-International Programs

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**MEDICAL
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If the tandem meetings of IBMTR/ABMTR and ASBMT (American Society for Blood and Marrow Transplantation) were successful in 1995 (and they were!), the 1999 Meetings should prove phenomenal. Back to back at Keystone Resort, participants of the 1999 IBMTR/ABMTR Participants' Meeting (February 28-March 3) and the 1999 Annual Meeting of the ASBMT (March 3-6) can once again optimize travel funds by attending two meetings in a single week. Program chairs for the Tandem Meetings (Dr. Daniel Weisdorf, University of Minnesota, Minneapolis, for the IBMTR/ABMTR and Dr. Richard Jones, Johns Hopkins University, Baltimore for the ASBMT) have planned a coordinated scientific program addressing key topics in the basic and clinical science of blood and marrow transplantation. About 1,000 attendees are expected.

The IBMTR/ABMTR Keynote Speaker is Robert E. Wittes, M.D., Director of the Division of Cancer Treatment, Diagnosis and Centers, at the National Institutes of Health. Dr. Wittes will discuss *Problems and Opportunities Facing Biomedical/Clinical Research in the Next Decade* on Monday, March 1.

An important addition to this year's agenda is an Advanced Statistics Workshop for Clinicians, conducted by Dr. John Klein, Statistical Director of the IBMTR/ABMTR, and Prof. Niels Keiding, University of Copenhagen.

All IBMTR/ABMTR Working Committees will meet to plan the next year's activities. Meetings are open to all interested in taking an *active* role in ongoing studies. All Working Committee members should plan to attend.

Physicians and scientists working in the field of blood and marrow transplantation have the opportunity to submit abstracts for presentation at either the IBMTR/ABMTR Poster Session or the ASBMT Poster Sessions. Late afternoon Poster Sessions will be combined with hosted receptions, featuring Keystone's award-wining light buffet-style cuisine and beverages.

Data management professionals will present their abstracts at a poster session on Monday, March 1 from 4:00-5:30 pm. Two of these abstracts will be selected for oral presentation during the Data Management Poster Session.

Data Management Workshops will be conducted on two tracks. While both will discuss current IBMTR/ABMTR Registration and Reporting procedures, Track 1 will review fundamental concepts for first-time attendees. Track II, designed for those who have attended previous Workshops, will emphasize special topics and roundtable discussions.

StemSoft Software Inc. will offer several training sessions during the Tandem BMT Meetings. Fees for participating in each session are $400. Sessions are limited to 40 participants each, and are subject to cancellation if less than half full. Contact Joan Sheehan at StemCell Software Inc. in Vancouver, BC (Canada) at ☎ 800-667-0322 or ☎ 604-877-0713, or stemsoft@stemcell.com.

Oncology Nursing Society (ONS) Workshops, supported by an unrestricted educational grant from Bristol-Myers Oncology, will be held mid-week, on Tuesday and Wednesday, March 2-3. Coordinated by Susan O'Connell, MSN, RN, OCN of the ONS BMSCT Special Interest Group, topics will include pharmacology of new agents used for blood and marrow transplant, quality of life, innovative approaches to symptom and homecare management of transplant patients, outpatient BMT, gene therapy, nursing research and ethical issues in transplantation.

For general questions about meeting format or registration, please contact: D'Etta Waldoch, CMP, Associate Director-International Programs, IBMTR/ABMTR, Medical College of Wisconsin at HRC Suite 2500, 8701 Watertown Plank Road, Milwaukee, WI 53226 USA; ☎414-456-8377; fax: 414-827-4997; email: detta@compuserve.com

> **SPECIAL ISSUE**
> **Report on State-of-the-Art in Blood and Marrow Transplantation with Guide to IBMTR/ABMTR Summary Slides**
> **(see pages 4-10)**
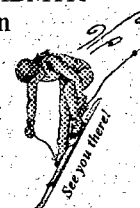
New Chair Sees Evolving and Dynamic Role for ABMTR Research Programs

The Autologous Blood and Marrow Transplant Registry continues to flourish as the following statistics aver. Since 1989, 254 participating centers in the United States, Canada, Mexico and South America registered a total of 42,496 patients with the Statistical Center. (Registration includes providing basic pre- and posttransplant clinical data.) In 1997, ABMTR centers registered 6,914 new patients. The distribution of autotransplants performed between 1992 and 1997 and registered with the ABMTR is shown in the table below. *Comprehensive* data are available on 11,921 (28%) autotransplants for specific diseases.

Twelve IBMTR/ABMTR Working Committees with 378 physicians voluntarily design, analyze and publish studies using this extensive database. In 1998, the ABMTR added a new subcommittee—Autoimmune Disease—chaired by Dr. Richard Burt, in response to rapidly increasing interest in the role of autotransplants in this area. A total of 90 IBMTR/ABMTR studies are at varying stages of completion; 40% involve autotransplants. Indeed, the process to initiate new studies has been so successful that a prioritization exercise was undertaken in 1998 to focus on the most compelling investigations.

This happy state of affairs reflects the outstanding contributions, guidance and wisdom provided by my predecessor, Jim Armitage. I am deeply honored to take over from Jim and not at all surprised that little in the way of a change in direction appears necessary at present. This does not mean that the ABMTR is static. This is far from the case. In fact, there is ample evidence that it is maturing and evolving rapidly and, in my view, appropriately. A good example is the increased interaction with the IBMTR through com-

bined scientific Working Committees. Additionally, closer collaborations underway with the American Society for Blood and Marrow Transplantation (ASBMT), the National Marrow Donor Program (NMDP) and the European Group for Blood and Marrow Transplantation (EBMT) are likely to be academically fruitful. The jointly planned Tandem Meetings of the IBMTR/ABMTR and ASBMT to be held in March 1999 is a case in point. It is becoming evident that all parties can derive benefit from such cooperation without any loss of identity and also fulfill their specific objectives to a greater extent than if they were to go it alone.

A further evolutionary change is the increased professionalism of fund-raising that has been thrust upon the ABMTR and IBMTR. While peer-reviewed grants from national agencies are the mainstay of our budget, particularly a major grant from the U.S. National Institutes of Health, they are insufficient for our needs and other sources of funds are urgently required. Susan Ladwig, the Associate Director of Development at the Statistical Center, has done an outstanding job in this regard and is coordinating a variety of new approaches to enhance fund-raising. Funds must cover not only the vital scientific activities of the Center, but also its well established and important educational role in assisting the profession and the public. Here, too, the tools are evolving—a new website is being launched this year that will provide easier access to information and solicit financial support.

It is clear that the ABMTR is a dynamic and evolving organization and, in this context as well, I have every confidence that its many active members will be willing to help meet the challenges that will undoubtedly face us in the next year and beyond.

Armand Keating, MD
Chair, Executive
Committee

ABMTR Executive Committee Chair, Dr. Armand Keating, MD, is Professor and Chief, Medical Services, Ontario Cancer Institute/ Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada

Distribution and frequencies of autotransplants performed between 1992 and 1997, and registered* with the ABMTR

Disease	1992 & 93	1994 & 95	1996 & 97**
Breast cancer	2779 (33)	4503 (40)	5695 (43)
Non-Hodgkin lymphoma	2446 (29)	2807 (25)	3082 (23)
Hodgkin lymphoma	965 (12)	1036 (9)	1106 (8)
Acute myelogenous leukemia	730 (8)	727 (6)	521 (4)
Multiple myeloma	357 (4)	742 (7)	1405 (10)
Acute lymphoblastic leukemia	172 (2)	168 (2)	124 (1)
Neuroblastoma	194 (2)	238 (2)	221 (2)
Testicular cancer	133 (2)	98 (1)	164 (1)
Ovarian cancer	131 (2)	273 (2)	322 (2)
Brain tumor	109 (1)	91 (1)	109 (1)
Chronic myelogenous leukemia	61 (1)	88 (1)	98 (1)
Other malignancy	340 (4)	436 (4)	579 (4)
Total	**8417**	**11207**	**13426**

Registration data includes basic pre- and posttransplant clinical information; comprehensive clinical data are collected on a subset of registered cases.

** *Data incomplete*

Expanded Information and Report Forms Now Available on the New IBMTR/ABMTR Web Site

This issue of the *ABMTR Newsletter* presents our **1998 Summary Slides on State-of-the-Art in Blood and Marrow Transplantation** and serves as an interpretation guide for their use. The slides will be sent to all IBMTR/ABMTR Participating Teams and to IBMTR/ABMTR Corporate Members early next year. This year's Summary Slides were supported by generous educational grants from **Ortho Biotech Inc**, **Cell Therapeutics, Inc.**, and **Pfizer Inc**. Based on feedback regarding previous editions, we anticipate these slides will be valuable educational and presentation tools.

the upcoming 1999 Tandem BMT Meetings, and listings of IBMTR/ABMTR Executive, Advisory and Working Committee members, Statistical Center personnel, publications, and participating centers. Future phases will add exciting new features and functionalities including Working Committee discussion rooms, on-line completion of IBMTR/ABMTR Registration forms, and additional information services features including disease-specific reports and statistical information.

We are also pleased to announce that the IBMTR/ABMTR web site will have its premier showing at the 1998 ASH Meetings in Miami, Florida. The web site was supported through a generous educational grant from **Searle**. The new site will feature the 1998 Summary Slides, current and past issues of the *IBMTR* and *ABMTR Newsletters*, Report Forms which can be printed directly from the site, information on

Please visit our website at www.ibmtr.org

supported by an unrestricted educational grant from Searle

In Memoriam

With great sadness, I would like to inform you of the death of Mrs. Barbara (Babs) H. Bortin, a valued member of the Statistical Center of the International Bone Marrow Transplant Registry who passed away on August 15, 1998, after a hard-fought battle against ovarian cancer. Mrs. Bortin was the wife of the late Mortimer M. Bortin, MD, founding Scientific Director of the International Bone Marrow Transplant Registry (IBMTR). Mrs. Bortin aided Dr. Bortin in his efforts in establishing and nurturing the IBMTR/ABMTR through its early years. She subsequently joined the IBMTR's data management staff in 1985 after retiring from a career with the Milwaukee Public Schools. She was a devoted supporter of the IBMTR and continued her work with the Statistical Center through much of her illness. Her expertise, kindness and friendship will be greatly missed. Anyone wishing to send the family condolences may do so by addressing them to the IBMTR/ABMTR Statistical Center, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA so they can be forwarded to her family. The family requests that donations in Mrs. Bortin's name be made to the Mortimer M. Bortin Memorial fund, which Mrs. Bortin helped establish.

Message from the Scientific Director

Mary M. Horowitz,
MD, MS
Scientific Director

Mary M. Horowitz, MD, MS is Scientific Director of the IBMTR/ABMTR and Professor of Medicine at the Medical College of Wisconsin

NEW SUMMARY SLIDES SHOW CURRENT TRENDS IN BMT

By J. Douglas Rizzo, MD, IBMTR/ABMTR Assistant Scientific Director

Since 1972 the International Bone Marrow Transplant Registry (IBMTR) has collected outcome data from blood and marrow transplant centers worldwide. More than 375 centers now participate. The IBMTR database includes information for about 40% of allogeneic bone marrow transplants done between 1970 and 1997. In 1991, the Autologous Blood & Marrow Transplant Registry (ABMTR) began collecting outcome data on autotransplants from centers in North and South America. More than 250 autotransplant centers now participate. The ABMTR database includes information for about 50% of autotransplants done in North and South America between 1989 and 1997.

Using these data, the Statistical Center periodically prepares and distributes slides summarizing current use and outcome of allogeneic and autologous hematopoietic stem cell transplants (SCT). This year's Summary Slides, made possible by generous educational grants from Pfizer Inc., Ortho Biotech Inc. and Cell Therapeutics, Inc., are described below.

Slide 1: Use of blood and marrow transplants continues to increase dramatically. We estimate 17,000 allogeneic and 30,000 autologous transplants were done in 1997.

Slides 2 & 3: Currently, 375 centers participate in the IBMTR worldwide, and 254 centers participate in the ABMTR. Numbers of participating centers continue to increase.

Slide 4: Most autotransplants use hematopoietic progenitor cells collected from blood. Fewer than 10% are done with bone marrow alone. Although over 70% of allografts still use bone marrow cells, use of allogeneic cells collected from peripheral blood increased significantly in the last few years to about 20% of the total. Though use is increasing, there are still relatively few transplants using umbilical cord blood cells.

Slides 5 & 6: For both allogeneic and autologous transplants, the proportion of patients over the age of 40 years at the time of transplant continues to increase. This may reflect advances in supportive care with resultant decreases in transplant-related toxicity and the application of transplant to dis-
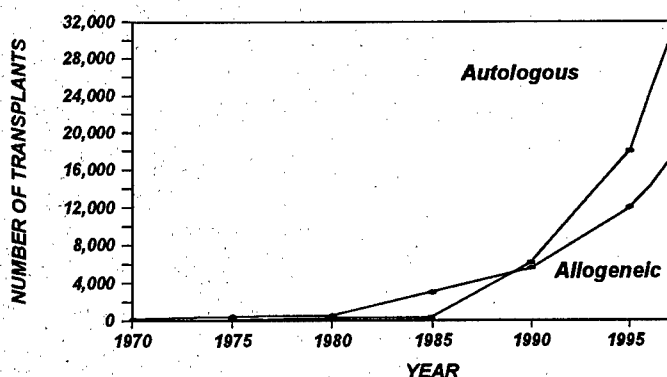
Slide 1. *Annual Number of Blood and Marrow Transplants Worldwide, 1970-1997*

Slide 2. *Location of Centers Participating in the IBMTR, 1998*

Plus,
Prahran, Australia
New Delhi, India
Rome, Italy
San Mateo, Mexico
Barcelona, Spain
Madrid, Spain
Pamplona, Spain
Cape Town, South Africa

Slide 3. *Location of Centers Participating in the ABMTR, 1998*
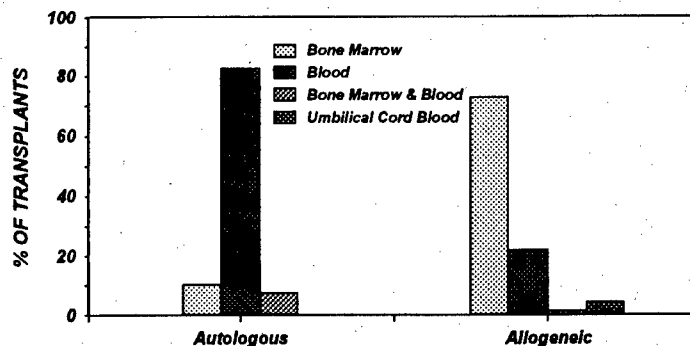
Slide 4. Stem Cell Sources, 1997

eases affecting older patients (e.g. multiple myeloma).

Slide 7: This slide illustrates indications for allogeneic and autologous stem cell transplants in North America. The most common indications for allogeneic and autologous transplants differ. For acute and chronic leukemias, myelodysplasia (MDS), and non-malignant diseases (aplastic anemia, immune deficiencies, inherited metabolic disorders), allogeneic transplant is the predominant approach. Autotransplants are used most commonly for breast, ovarian and other solid malignancies, Hodgkin and non-Hodgkin lymphomas and multiple myeloma. Breast cancer remains the most common indication for SCT in North America, accounting for nearly

one third of all transplants. Non-Hodgkin lymphoma is the second most common indication, followed by acute myelogenous leukemia (AML) and multiple myeloma.

Slide 8: Most allogeneic transplants are from HLA-identical sibling donors. However, only about 30% of transplant candidates have such a donor. Increasing availability of HLA-typed volunteer donors through large national and international registries has led to increasing use of unrelated donors for bone marrow transplants. Transplants from unrelated donors now account for about 25% of allogeneic transplants.

Slide 9: Leukemia remains the most common indication for allogeneic stem cell trans-

plantation worldwide. CML and AML each account for nearly one third of the allogeneic transplants performed throughout the world. Lymphoma, MDS/myeloproliferative syndromes, aplastic anemia and other non-malignant diseases each comprise approximately 10% of allogeneic transplants.

Slides 10 & 11: 100-day mortality is often used as a gauge of procedure-related toxicity. Allogeneic transplants are associated with relatively high risks of graft-versus-host disease (GVHD), infections and liver toxicity, resulting in high early mortality. Among HLA-identical sibling transplants done in 1996-97 and reported to the IBMTR, 100-day
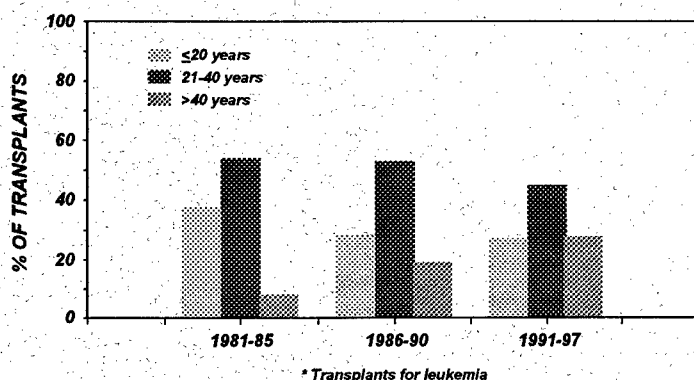
Slide 5. *Trends in Allogeneic BMT Recipient Age*, 1981-1997*
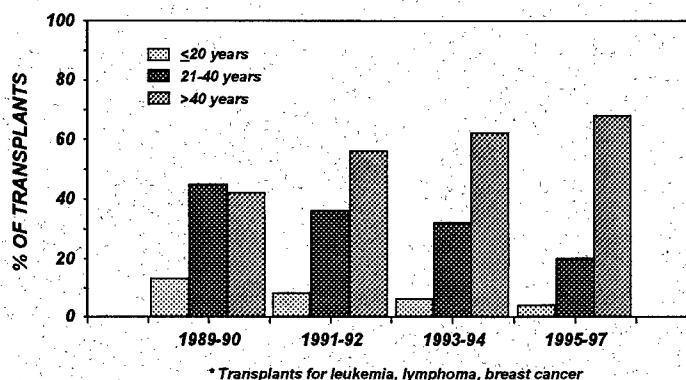
Slide 6. *Trends in Autologous Transplants Recipient Age*, 1989-1997*
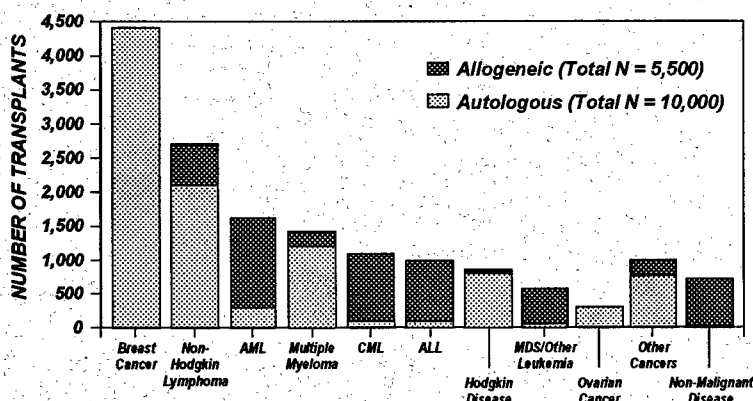
Slide 7. *Indications for Blood and Marrow Transplantation in North America, 1997*
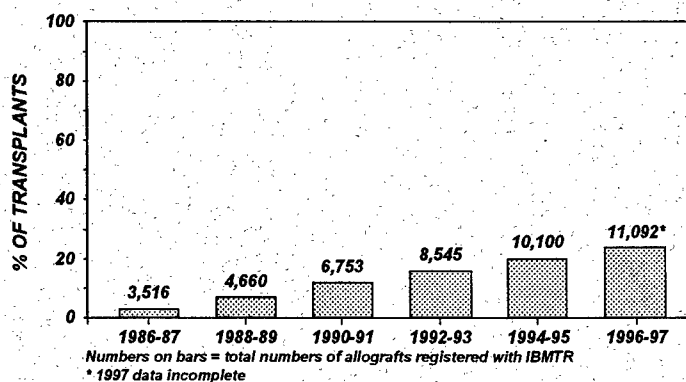
Slide 8. *Percent of Allogeneic Transplants from Unrelated Donors*

mortality rates range from about 10% for persons with acute leukemia in first remission to almost 40% for those with advanced leukemia. 100-day mortality rates in aplastic anemia and immune diseases range between 10% and 15%. Recurrence or progression of primary disease is responsible for nearly 40% of all deaths following HLA-identical sibling transplants, with GVHD and infection each responsible for 20% of deaths.

Slides 12 & 13: Early mortality is generally lower following auto- than allotransplants. Among patients receiving autotransplants in 1996-97, those treated for stage II/III breast cancer had 100-day mortality rates of <5%, while patients treated for acute leukemia not in remission had >20% early mortality. Pri-

mary disease recurrence accounts for the great majority of deaths in autotransplant recipients.

Slide 14: CML is the most frequent indication for allogeneic bone marrow transplantation worldwide. Among 3,703 recipients of HLA-identical sibling transplants done between 1990 and 1996, reported to the IBMTR, 3-year probabilities of survival were 67 ± 2% for 2,308 transplants performed within 1 year of diagnosis and 59 ± 3% for 1,395 patients transplanted more than one year after diagnosis.

Only about 30% of persons with CML have an HLA-identical sibling donor. Unrelated donor transplants can cure CML but are associated with higher risks of GVHD and

transplant-related mortality. Additionally, unrelated donor transplants are often delayed because of the time required to identify a donor and reluctance to risk the higher transplant-related mortality. Delaying transplantation may adversely affect outcome. For patients receiving unrelated donor transplants, the 3-year probabilities of survival were 51 ± 7% for 278 patients transplanted within the first year of diagnosis, and 40 ± 4% for 773 patients transplanted beyond the first year.

Slide 15: Results of HLA-identical sibling transplants for AML correlate with remission state. Among 3,581 recipients of HLA-identical sibling transplants for AML performed between 1990 and 1996, reported to the
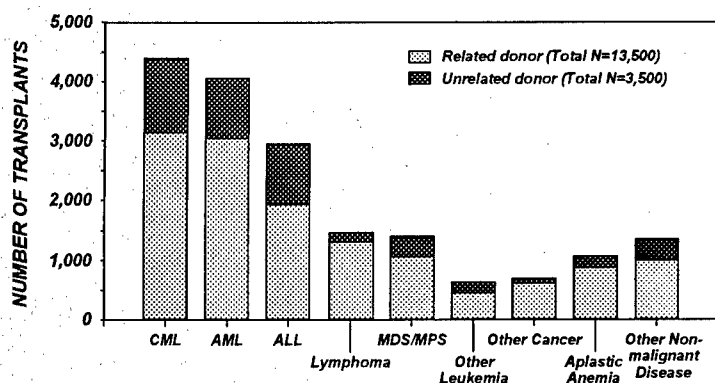
Slide 9. *Indications for Allogeneic Blood and Marrow Transplantation Worldwide, 1997*
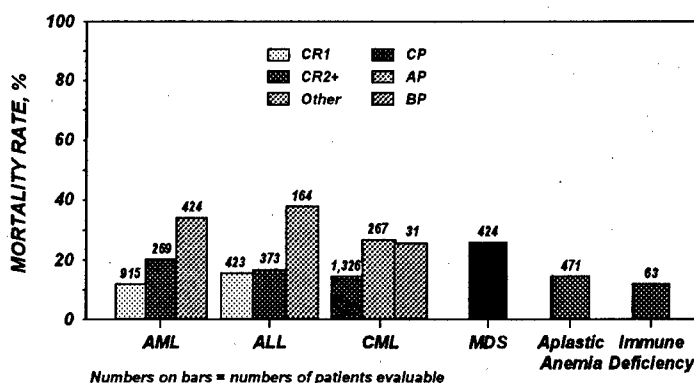
Slide 10. *100-day Mortality after HLA-identical Sibling Transplants, 1996-1997*
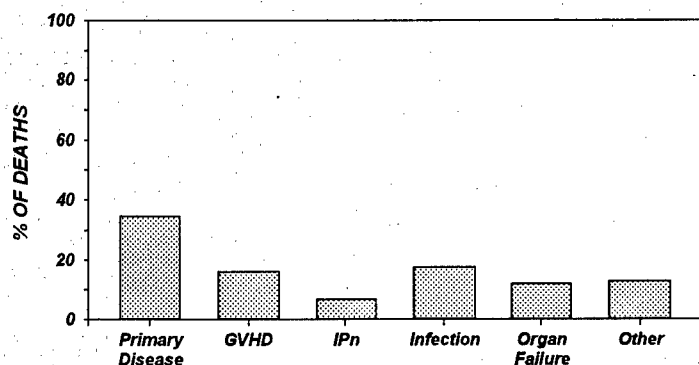
Slide 11. *Causes of Death after HLA-identical Sibling Transplants, 1990-1997*
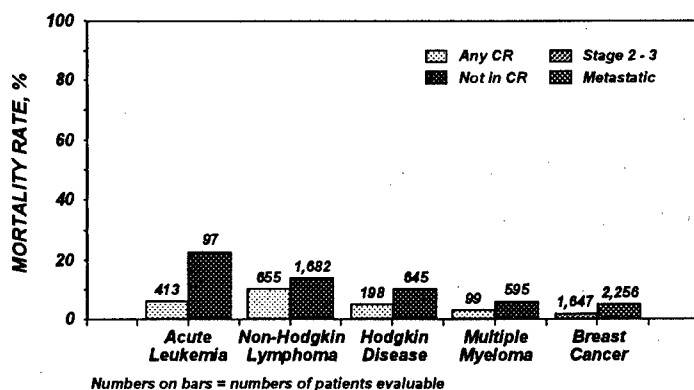
Slide 12. *100-day Mortality after Autotransplants, 1996-1997*

IBMTR, 3-year probabilities of survival were 63% ± 2% for 2,917 transplants in first remission, and 44 ±4% for 664 patients in second or subsequent remission. Survival was generally worse in patients receiving transplants from unrelated donors. Recipients of unrelated donor transplants in first remission had a 3-year probability of survival of 50 ±8%, while those in second remission or greater had a 3-year probability of survival of 36 ±8%.

Slide 16: Among patients receiving autologous transplants for AML between 1990 and 1996, reported to the ABMTR, the 3-year probabilities of survival were 57±3% for 1,030 patients in first remission at time of transplant, 40 ±5% for 453 in second remission,

and 22 ±7% for 201 patients not in remission at time of transplant.

Slide 17: Most patients with ALL are cured with conventional chemotherapy. Consequently, bone marrow transplants are generally reserved for patients failing conventional therapy, i.e., in relapse or second or subsequent remission, or patients in first remission with prognostic factors predicting a high risk of failure with conventional therapy. The most frequent indications for transplants in first remission are older age, high leukocyte count at diagnosis, Ph^1 and other chromosome abnormalities and difficulty obtaining a first remission. Among 2,611 recipients of HLA-identical sibling transplants between 1990 and 1996, reported to the IBMTR, 3-year

probabilities of survival were 56 ± 3% for 1,314 transplants done in first remission and 44 ± 3% for 1,297 in second or subsequent remission.

Although associated with higher transplant-related mortality, unrelated donor transplants may be considered for patients with ALL unlikely to be cured with chemotherapy. Among patients transplanted in second remission, there is little difference in overall survival between HLA-identical sibling and unrelated donor transplants, since higher GVHD rates are offset by lower relapse rates after unrelated donor transplants. Among 186 recipients of unrelated donor transplants
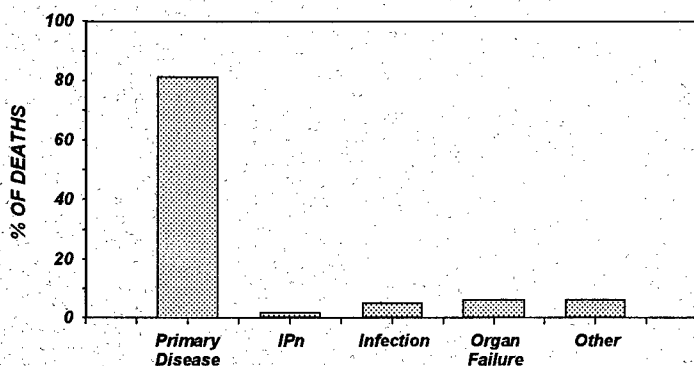
Slide 13. *Causes of Death after Autotransplants, 1990-1997*
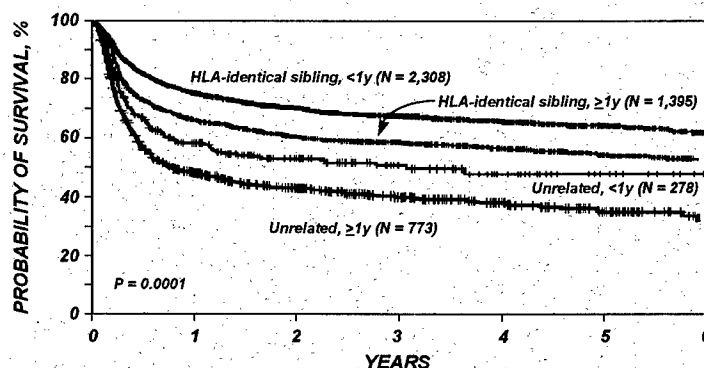
Slide 14. *Probability of Survival after BMT for CML in Chronic Phase by Donor Type and Disease Duration, 1990-1996*
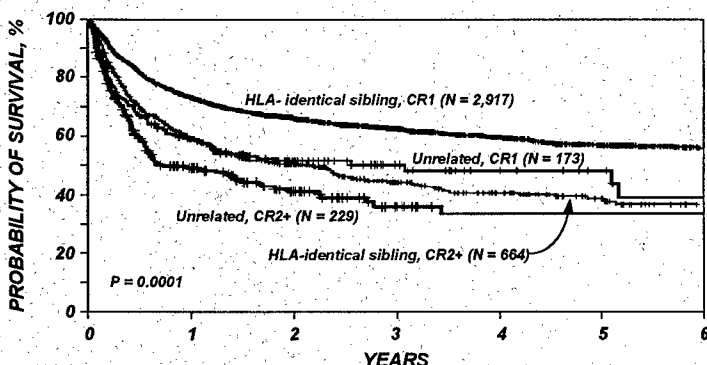
Slide 15. *Probability of Survival after Allogeneic BMT for Acute Myelogenous Leukemia by Donor Type and Remission Status, 1990-1996*
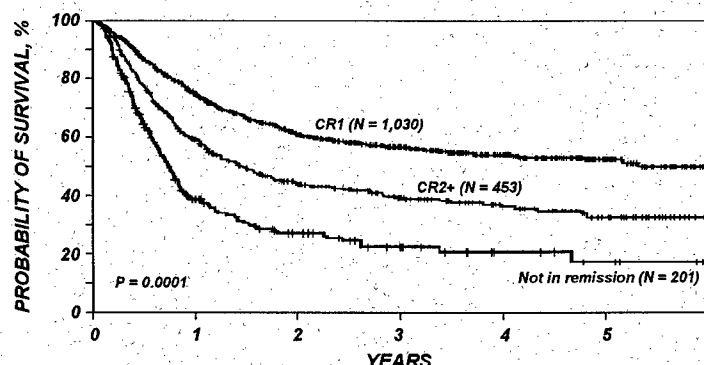
Slide 16. *Probability of Survival after Autotransplants for Acute Myelogenous Leukemia, 1990-1996*

for ALL in first remission reported to the IBMTR, 3-year probability of survival was 46 ± 8%; among 517 receiving unrelated donor transplants in second or subsequent remission, it was 36 ± 7%.

Slide 18: Among 399 recipients of autotransplants for ALL between 1990 and 1996, reported to the ABMTR, 3-year probabilities of survival were 47 ± 10% for 139 transplants done in first remission, 35 ± 7% for 227 done in second or subsequent remission, and 14 ± 14% for 33 done in relapse.

Slide 19: Allogeneic bone marrow transplantation can cure some patients with myelodysplastic syndromes. For 238 patients receiving HLA-identical sibling trans-

plant between 1990 and 1996 for refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) at time of transplant, survival probability at 3 years was 53 ± 7%. For 633 patients with refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), or chronic myelomonocytic leukemia (CMML), 3 year probability of survival was 37 ± 4%.

Slide 20: Allogeneic transplantation is the treatment of choice for young patients with aplastic anemia who have an HLA-identical sibling. 3-year probabilities of survival after 1,608 HLA-identical sibling transplants between 1990 and 1996, reported to the IBMTR, were 76 ± 3% for 825 patients <20 years of

age and 66 ± 4% for 783 patients older than 20 years. Results were not as good in 266 recipients of unrelated donor transplants: 49 ± 8% in 183 patients <20 years and 33 ± 10% in 83 older patients.

Slide 21: Most patients with Hodgkin disease are cured with conventional chemotherapy. However, for the 20-30% failing conventional therapy, autotransplants are effective salvage therapy. Among 2,331 autotransplants between 1990 and 1996, reported to the ABMTR, 3-year probabilities of survival were 51 ± 6% for 428 patients never in remission, 84 ± 9% for 88 patients transplanted in first remission, 58 ± 3% for 549 transplants in first relapse and 78 ± 4% for 1,266 patients transplanted in second or
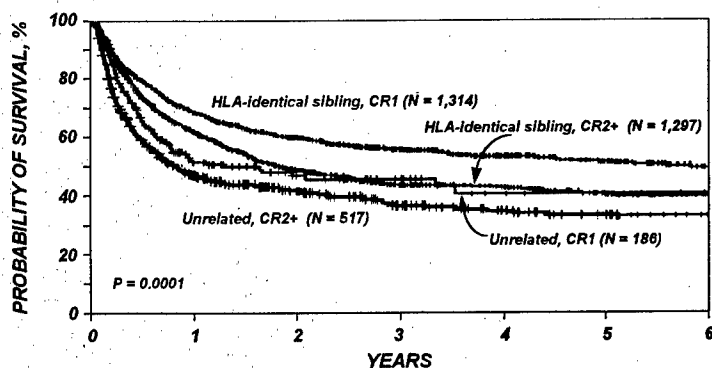
Slide 17. *Probability of Survival after Allogeneic BMT
for Acute Lymphoblastic Leukemia by
Donor Type and Remission Status, 1990-1996*
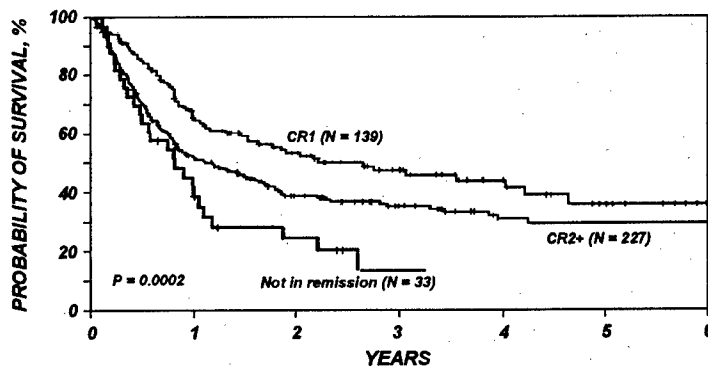
Slide 18. *Probability of Survival after Autotransplants
for Acute Lymphoblastic Leukemia, 1990-1996*
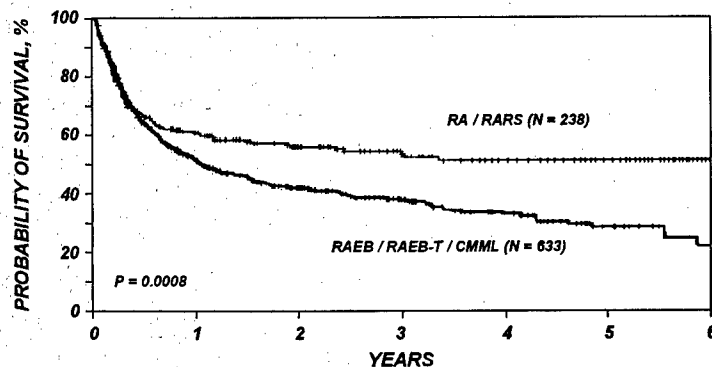
Slide 19. *Probability of Survival after HLA-identical
Sibling Transplants for Myelodysplastic
Syndromes, 1990-1996*
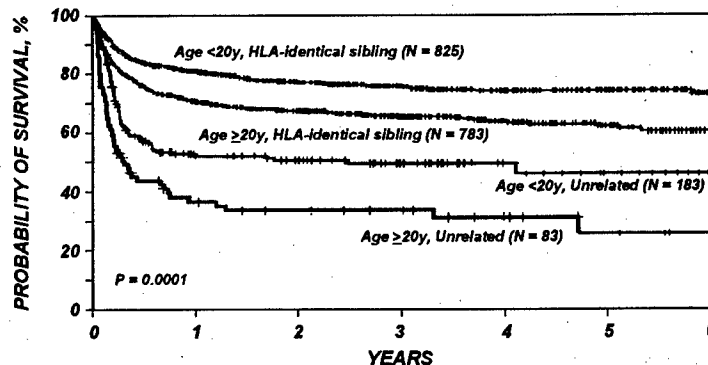
Slide 20. *Probability of Survival after Allogeneic BMT
for Severe Aplastic Anemia
by Age and Donor Type, 1990-1996*

subsequent remission. Relapse is less frequent but treatment-related mortality is higher with HLA-identical sibling transplants, with 3-year probability of survival of approximately 50% in 216 patients, regardless of stage.

Slides 22 & 23: Autotransplants are also commonly used for non-Hodgkin lymphoma (NHL). Among 878 patients receiving autotransplants for low-grade NHL, 3-year probabilities of survival were 78 ± 11% for 104 patients in first remission, 65 ± 5% for 442 in first relapse, 75 ± 11% for 105 in second remission and 60 ± 8% for 227 never achieving remission with standard chemotherapy.

Slides 24 & 25: Among 2,814 patients receiving autotransplants for intermediate grade or immunoblastic NHL, 3-year probabilities of survival were 70 ± 6% for 289 patients in first remission, 40 ± 3% for 1,298 in first relapse, 52 ± 5% for 502 in second remission and 42 ± 4% for 725 never achieving remission with conventional chemotherapy. Most failures after autotransplants for NHL are due to relapse. 3-year survival rates after HLA-identical sibling transplants for these lymphomas were 39 ± 15% for 46 patients in first or second remission, 30 ± 10% for those not achieving remission (n=107), and 26 ± 10% for 116 patients transplanted in relapse.

Slides 26 & 27: Stem cell transplantation is increasingly used for multiple myeloma, a disease considered incurable with conventional therapy. 3-year survival after HLA-identical sibling transplants reported to the IBMTR between 1990 and 1996 was 37 ± 3% regardless of duration of myeloma at the time of transplant. For 836 patients receiving autologous transplant within 18 months of diagnosis of myeloma, 3-year survival was 53 ± 5%. It was 40 ± 7% for 290 patients receiving autotransplants longer than 18 months after diagnosis.
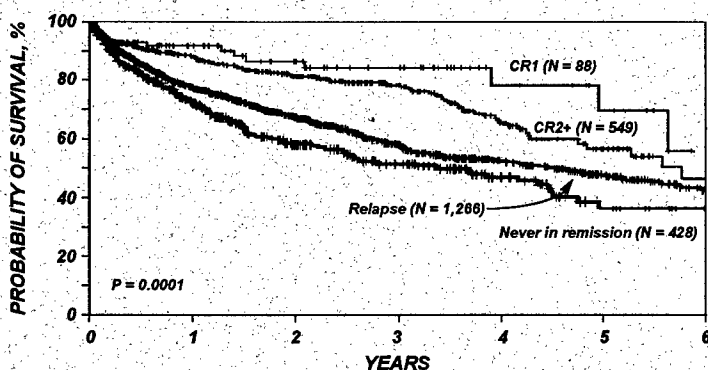
Slide 21. *Probability of Survival after Autotransplants for Hodgkin Disease, 1990-1996*
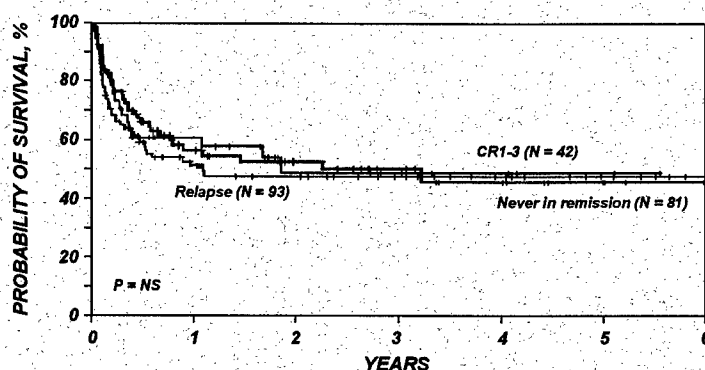
Slide 22. *Probability of Survival after HLA-identical Sibling BMT for Low Grade Non-Hodgkin Lymphoma, 1990-1996*
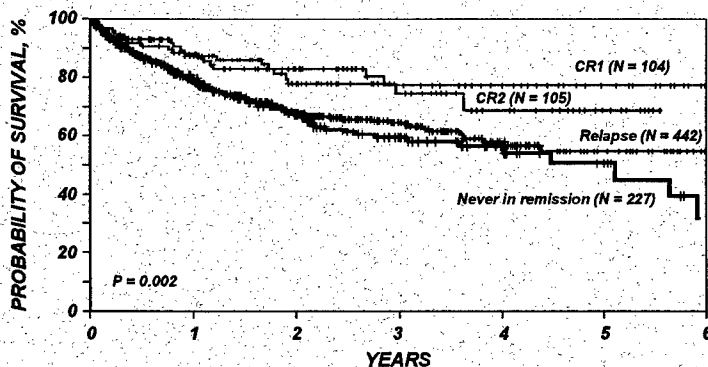
Slide 23. *Probability of Survival after Autotransplants for Low Grade Non-Hodgkin Lymphoma, 1990-1996*
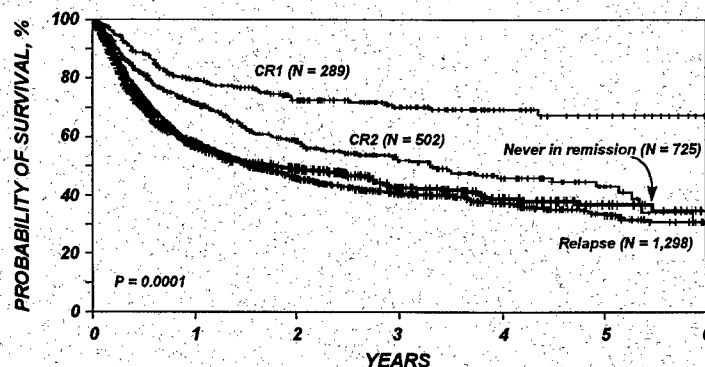
Slide 24. *Probability of Survival after Autotransplants for Intermediate Grade or Immunoblastic NHL, 1990-1996*

(continued from previous page)

Slides 28 & 29: Breast cancer is the most frequent indication for autotransplant in North America. Among 9,162 women receiving autotransplants for breast cancer between 1990 and 1996 and reported to the ABMTR, 3-year probabilities of survival were 75 ± 3% in 1,536 women with Stage 2 disease, 68 ± 4% in 1,366 women with Stage 3 disease, 55 ± 6% in 570 women with inflammatory breast cancer and 33 ± 2% in 5,690 women with metastatic breast cancer. Outcome in metastatic breast cancer was significantly better for women who achieve a complete remission with conventional therapy prior to transplant. Among the 4,657 women transplanted for metastatic disease in whom pretransplant response to chemotherapy was known, 3-year probability of survival was 48 ± 3% in 1,401 with a complete response, 30 ± 2% in 2,330 with a partial response and 19 ± 3% in 926 women with resistant disease.

Slide 25. *Probability of Survival after HLA-identical Sibling BMT for Intermediate Grade or Immunoblastic NHL, 1990-1996*

Slide 26. *Probability of Survival after HLA-identical Sibling BMT for Multiple Myeloma by Disease Duration, 1990-1996*

Slide 27. *Probability of Survival after Autotransplants for Multiple Myeloma by Disease Duration, 1990-1996*

Slide 28. *Probability of Survival after Autotransplants for Breast Cancer, 1990-1996*

Slide 29. *Probability of Survival after Autotransplants for Metastatic Breast Cancer by Pretransplant Chemosensitivity, 1990-1996*

FOUNDATION AND CORPORATE SUPPORT OF THE IBMTR / ABMTR

All of us at the IBMTR/ABMTR Statistical Center thank the many contributors who have joined our international collaboration for research in blood and marrow transplantation. Private support for the Registries continues to be vitally important since federal grants cover only 50 percent of the Statistical Center's budget. We gratefully acknowledge the support of the Medical College of Wisconsin; the National Cancer Institute; the National Institute of Allergy and Infectious Disease; the National Heart, Lung and Blood Institute; the Department of Defense; and the generosity of the following foundations and corporations:

Non-Federal Support Listing for the IBMTR / ABMTR
(Grant Awards Since 1997)

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IBMTR / ABMTR CORPORATE MEMBERSHIP PROGRAM

Several corporations have joined the IBMTR/ABMTR Corporate Membership Program (see above). The annual membership program provides member organizations with informational materials on blood and bone marrow transplantation developed by the IBMTR/ABMTR Information Resource Service.

The program includes subscriptions to the *Statistical Center Report on Survival Statistics for Blood and Marrow Transplants, IBMTR and ABMTR Newsletters,* the worldwide *IBMTR/ABMTR Directory of Blood and Marrow Transplant Teams,* and the *IBMTR/ABMTR Summary Slides on State-of-the-Art in Blood and Marrow Transplantation* as well as invitations to our meetings and educational forums and access to the IBMTR/ABMTR databases for simple analyses. These resources are useful for marketing managers, medical directors, research directors, product managers, case managers or transplant coordinators.

For additional information on the Corporate Membership Program, please contact Susan Ladwig, Associate Director of Development ☎ (414) 456-8363, Fax: (414) 456-6530.

**By
Susan Ladwig, MA
Associate Director
of Development,
Statistical Center**

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COMMUNITY RESPIRATORY VIRAL INFECTIONS IN THE POSTTRANSPLANT PATIENT

by Richard E. Champlin, MD
M. D. Anderson Cancer Center, Houston, Texas

Infection is a common and often life-threatening problem in the first year after blood and bone marrow transplantation. Multiple bacterial, fungal and viral organisms are implicated, many not serious pathogens except in settings of compromised immune function. Strategies for preventing and treating gram-negative and gram-positive bacterial infections, fungal infections and herpes virus infections such as cytomegalovirus receive much attention; improved management of these infections contributes to recent decreases in transplant-related mortality. The importance of common respiratory viruses, such as respiratory syncytial virus (RSV), influenza, parainfluenza, rhinoviruses, adenoviruses and coronaviruses, in causing severe illness in transplant recipients is less well understood.

IBMTR/ABMTR ANNUAL PARTICIPANTS' MEETING in Keystone, Colorado on January 8-14, 1998

by D'Etta Waldoch Severson, CMP, IBMTR/ABMTR Associate Director-International Programs

The 1998 Annual Participants' Meeting will combine a stimulating scientific program, 13 Working Committee meetings, a beautiful venue and some of the best skiing available in Colorado. Plenary and Simultaneous Scientific Sessions will be presented by more than 75 speakers representing 10 countries. Topics include evaluation of minimal residual disease, ex vivo expansion of stem cells, biology of dendritic cells, immunotherapy in the transplant setting, cord blood and peripheral blood allografts and posttransplant infections. Sessions will be held in the morning and evening, allowing time in the afternoon for participants to enjoy a variety of winter recreational activities at Keystone.

The 1998 Keynote Address, *The Other Side of Health Care—A Physician Treated by Transplantation*, will be given by Dr. Richard Boxer on Sunday, January 11, at the opening reception. Dr. Boxer, a national leader in health care reform and a practicing urologist, received an autotransplant for non-Hodgkin lymphoma at the University of Nebraska in Omaha. On Monday, January 12, the late afternoon reception will be combined with an IBMTR/ABMTR Poster Session. The $500 Mortimer M. Bortin Research Award will be given for the best abstract submitted.

Data Management Workshops will be held on Friday, January 9. Sessions on scoring common toxicities, and overviews of statistical analyses, high-dose therapies and audit survival tactics will provide practical guidelines for those working with clinical data and the Statistical Center. $500 grants from the US Department of Defense will be awarded to 30 eligible data managers to offset travel costs associated with attending the Workshops. StemCell Technologies Inc will offer three full-day training sessions at Keystone, January 10-12. The fee for participating in each session is $400. Those interested may contact Ellen Low at ☎ 800-667-0322 or ☎ 604-877-0713, or stemsoft@stemcell.com.

Friday evening and Saturday, January 9-10, are devoted to a series of excellent corporate-supported Satellite Sessions. Breakfast on Sunday, Monday and Tuesday will feature Satellite Poster Sessions, and a luncheon Satellite Session will be held on Monday.

The IBMTR/ABMTR Steering Committees will meet for the first time at Keystone, as well as the Executive, Advisory and Working Committees. The five-day meeting will conclude on Wednesday, January 14, at noon.
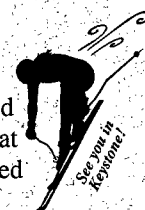
Register Early!
More than 500 participants are expected to attend the 1998 Annual Meeting at Keystone. Participants are encouraged to make hotel reservations soon.
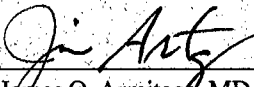
> **For meeting information, contact D'Etta at the Statistical Center:**
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Message from the Scientific Advisory Committee Chair

James O. Armitage, MD
Chair, Scientific Advisory Committee

The ABMTR Continues As a Unique Resource for Studying the Growing Use of Autologous Transplantation

The Autologous Blood & Marrow Transplant Registry (ABMTR) continues to grow. Currently, 220 participating centers in the United States, Canada, Mexico and South America provide data to the Registry. More than 100 physicians from these centers volunteer their time to serve on one or more ABMTR Working Committees, to plan and conduct studies using these data.

In the past year, ABMTR centers registered over 7,000 new patients. The total number of transplants available for study exceeds 30,000. The distribution of diseases treated by those transplants is shown below.

These data are being used to conduct an increasing number of studies. The ABMTR has active investigations in autotransplants for breast cancer, non-Hodgkin and Hodgkin lymphoma and ovarian cancer. Disease-specific Report Forms are recently complete or near completion for multiple myeloma, neuroblastoma, lung cancer and CNS tumors. Data collected on these forms will allow additional studies in the near future. The Registry continues to be a unique resource for studying the impact of high-dose therapy on management of patients with diverse disorders.

This issue of the Newsletter focuses on RSV (respiratory syncytial virus) and other community respiratory viral infections in the bone marrow transplant setting, an increasingly recognized problem in immune suppressed patients. Understanding the epidemiology and manifestations of these infections in the posttransplant patient is important to allow early treatment. Registry studies to provide insight into the prevalence and natural history of community respiration infections are planned. The Newsletter also summarizes a new ABMTR study on autotransplants for neuroblastoma, funded in part by the Eppley Foundation for Research in New York.

On behalf of the Registry, I want to express thanks to all those whose efforts make this program a success.

ABMTR Advisory Committee Chair, James O. Armitage, MD, is Professor and Chairman, Department of Medicine, University of Nebraska Medical Center, Omaha. Dr. Armitage served as President of the American Society for Clinical Oncology (1996-1997).

Distribution of autotransplants performed between 1989 and 1996, registered with the ABMTR by 220 teams in North and South America

Disease	Totals, %
Breast cancer	10,556 (35)
Non-Hodgkin lymphoma	7,653 (25)
Hodgkin lymphoma	3,593 (12)
Acute myelogenous leukemia	2,330 (8)
Acute lymphoblastic leukemia	590 (2)
Chronic myelogenous leukemia	271 (1)
Multiple myeloma	1,715 (6)
Neuroblastoma	735 (2)
Ovarian cancer	695 (2)
Testicular cancer	452 (1)
Brain tumor	370 (1)
Lung cancer	128 (<1)
Bone sarcoma	118 (<1)
Other cancer	1,189 (4)
Total	30,395

The IBMTR/ABMTR Statistical Center Celebrates Achievements: 1972-1997

This year was a very special one for the IBMTR/ABMTR Statistical Center. First, we celebrated the 25th anniversary of the IBMTR. On September 13 over 200 physicians and scientists from around the world joined us at the Medical College of Wisconsin for our 25th Anniversary Educational Symposium on *New Directions in Blood Cell and Bone Marrow Transplants.* Speakers addressed issues of stem biology, alternative sources of stem cells for transplantation, gene therapy and xenotransplantation. Almost 300 friends and supporters shared a gala dinner program that evening, featuring comments by Dan Rutz of CNN News and a keynote speech by Wisconsin First Lady Sue Ann Thompson (see p. 6). We were very pleased to have three of the IBMTR's founders join us for the celebration: Dr. Robert Good of All Children's Hospital, St. Petersburg, Florida; Professor Georges Mathé of the Institut de Cancerologie et d'Immunologie, Villejuif, France; and Dr. George W. Santos of The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Second, I am happy to announce, the National Institutes of Health intends to award an R24 grant to support the IBMTR and ABMTR for 1998-2003. This grant will provide about 60 percent of the funds needed for our scientific and educational programs. The remaining funds must come from foundation, corporate and individual donations.

Third, accrual to the database reached an all-time high. The Statistical Center received about 7,000 initial Report Forms for transplant recipients during the past year, an increase of more than 2,000 compared to the year before!

Finally, five IBMTR/ABMTR studies were accepted for presentation at this year's annual meeting of the American Society of Hematology (ASH), December 5-9, 1997, San Diego, California.

Dr. Julie Vose (University of Nebraska, Omaha) will present results of autotransplants in patients with aggressive non-Hodgkin lymphoma failing primary induction therapy. This study of 221 patients failing to achieve a first complete remission with conventional therapy demonstrates 100-day mortality of $17 \pm 5\%$ (95% confidence interval) with 3-year progression-free and overall survival of $32 \pm 6\%$ and $40 \pm 7\%$, respectively. The only predictor of autotransplant outcome was sensitivity to prior chemotherapy. Patients with resistant disease had a 3-year probability of survival of only $19 \pm 12\%$ compared to $48\% \pm 13\%$ for those with sensitive (partial response) disease.

Dr. Martin S. Tallman (Northwestern University, Chicago) will present a study of the effect of high-dose cytarabine, given for consolidation of acute myelogenous leukemia in first remission, on outcome of subsequent HLA-identical sibling transplants. The study includes 77 patients receiving no postremission therapy prior to transplant, 151 receiving high-dose cytarabine and 239 receiving other consolidation therapy including cytarabine at standard dose. Preliminary analyses indicate no differences in relapse, transplant-related mortality or survival.

Dr. Stella Davies (University of Minnesota, Minneapolis) will present a comparison of total body irradiation (TBI) or busulfan with cyclophosphophamide for pretransplant conditioning in children transplanted in first or second remission. Multivariate analyses show increased treatment-related mortality and lower leukemia-free survival in the children receiving TBI.

Dr. Jakob Passweg (Kantonsspital Basel, Switzerland) will present an analysis of bone marrow transplant for severe aplastic anemia using unrelated or HLA-mismatched related donors. Five-year probabilities of survival in this cohort of 240 patients transplanted between 1985 and 1995 are $37 \pm 7\%$.

Dr. Philip Rowlings (Medical College of Wisconsin, Milwaukee) will present 8 cases of Hodgkin Disease developing after an allogeneic bone marrow transplant for leukemia or aplastic anemia. The observed-to-expected (in the general population) incidence ratio of Hodgkin Disease in transplant recipients was 6.31 (95% confidence interval 2.7-12). In contrast to other posttransplant lymphoproliferative disorders, these tumors developed relatively late and were not associated with T-cell depletion of donor marrow, use of antilymphocyte globulin or donor-recipient mismatch. In situ hybridization studies suggested presence of Epstein Barr virus in at least half of these cases.

These studies indicate the diversity and importance of issues addressed using the IBMTR/ABMTR database. Thank you for your continued participation in IBMTR/ABMTR research and educational programs. Through your help, we have been able to make a significant impact on the success of blood and marrow transplantation over the past 25 years.

Mary M. Horowitz, MD, MS
Scientific Director

Mary M. Horowitz, MD, MS is Scientific Director of the IBMTR/ABMTR and Professor of Medicine at the Medical College of Wisconsin

ABMTR INITIATES STUDY OF AUTOTRANSPLANTS FOR NEUROBLASTOMA

By Philip A. Rowlings, MD, MS, IBMTR/ABMTR Assistant Scientific Director

Neuroblastoma is the most common extra-cranial solid tumor of children accounting for 8%-10% of childhood malignancies. In the United States, between 500 and 1,000 children are diagnosed with neuroblastoma each year. Eighty-five percent are less than six years old at the time of diagnosis. Stage of disease and age at diagnosis are the major determinants of treatment outcome. Clinical staging of neuroblastoma is based on the extent of the primary tumor and sites of metastases. A set of uniform criteria for diagnosis, staging, and response to therapy were recently published (1). About 40% of children are cured with surgery, radiation and/or chemotherapy. Conventional treatments fail in the remaining 60%.

Published results of autotransplants in relatively small numbers of patients with high risk neuroblastoma are encouraging, showing disease-free survival rates of 30-50% (2). The ABMTR database has information for over 700 autotransplants for neuroblastoma. By analyzing large numbers of patients, the study should provide a more precise estimate of outcome in groups defined by well-characterized prognostic factors.

The study will also examine patient-, disease- and treatment-related variables for their association with transplant outcome. Of particular interest is the relative efficacy of high-dose conditioning regimens and approaches to graft purging. Also, because ABMTR centers provide continuing follow-up information on long-term survivors, the study will attempt to define the risk of late effects such as second cancers. In collaboration with the Pediatric Oncology Group, a quality of life questionnaire will also be developed to assess functional status of long-term survivors of autotransplants for neuroblastoma. Finally, in collaboration with the IBMTR, the study will compare the outcome of autologous and allogeneic transplants for neuroblastoma.

The first step in this study, development of a Disease-Specific Report Form for data collection was recently completed, with the help of a generous grant from the New York-based Eppley Foundation for Research. Centers who have submitted information regarding their neuroblastoma patients on older versions of the Report Forms will be asked to submit a supplemental form to provide all of the information required for the planned studies. We encourage you to submit the brief supplemental form as quickly as possible.

The study, which is under the auspices of the IBMTR/ABMTR Pediatric Cancer Working Committee (Chair, Bruce Camitta), will be chaired by Naynesh R. Kamani, MD, Director, Pediatric Bone Marrow Transplantation at the University of Texas Health Science Center in San Antonio. Individuals who wish to participate in this study or have questions may contact the IBMTR/ABMTR Statistical Center or Dr. Naynesh Kamani, Director, Pediatric Bone Marrow Transplantation, Division of Hematology/Oncology/Immunology, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284, ☎ (210) 704-3450 or fax (210) 704-2396, email: nkamani@srhcc.org.

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Reprints available on request

Infection with community respiratory viruses in immune competent persons is common though generally not serious, the most frequent syndrome being the "common cold." Except in the elderly and newborn, community respiratory virus infections generally involve only the upper respiratory tract and are self-limited in immune competent individuals.

A recent study at the M.D. Anderson Cancer Center (MDACC), examining nasal and throat specimens in leukemia and transplant patients presenting with respiratory symptoms, demonstrated community respiratory viruses in 27%. Viral prevalence in this study mirrored that in the community except that RSV was more common than might be expected. RSV was, in fact, the most common respiratory virus isolate. RSV infections occurred primarily in the winter and early spring. In contrast to respiratory virus infections in immune competent persons, such infections in transplant recipients frequently progressed to pneumonia after an upper respiratory prodrome. In MDACC studies, RSV was associated with pneumonia in about half of patients infected in the first year after an allogeneic bone marrow transplant; more than half of RSV pneumonias were fatal.

Strategies for preventing morbidity and mortality from community respiratory viruses require better awareness of their prevalence, prevention of nosocomial transmission, im-

munization and early diagnosis and treatment. Several studies demonstrate that respiratory viruses are frequently transmitted nosocomially, often from persons with only mild symptoms of illness. Strict adherence to infection control measures, that include contact isolation and prevention of exposure to persons with even mild respiratory illnesses,

> *"...successful treatment [of community respiratory virus infections] requires early diagnosis and intervention."*

can decrease nosocomial risk. Immunization is available only for influenza virus; patients, family members and health care workers should be vaccinated yearly. Passive immunization with immune globulin may be helpful for some viruses, including RSV. Effective antivirals are available for influenza A (amantadine, rimantidine) and RSV (ribavirin). However, successful treatment requires early diagnosis and intervention. This requires awareness of the prevalence of these viruses in the community and appropriate investigation of respiratory symptoms.

Although it is well-proven that community respiratory viruses can cause severe pulmo-

nary infection and death in transplant recipients, their overall contribution to early and late mortality after blood and marrow transplantation is still unclear. Most studies are limited by small numbers, inadequate sampling and restriction to patients with severe respiratory symptoms. The IBMTR/ABMTR will be exploring this area over the next few years, first by examining the seasonal incidence of fatal and non-fatal respiratory infections. We are particularly interested in whether interstitial pneumonias reported as idiopathic are associated with known patterns of viral prevalence in the community. With better understanding of the natural history of these disorders, hopefully progress can be made in prevention, diagnosis and treatment strategies.

Suggested Reading:

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IBMTR/ABMTR MEMBER PROFILE: Richard E. Champlin, MD

Richard E. Champlin, MD is Professor of Medicine and Chairman of the Department of Hematology at the University of Texas M.D. Anderson Cancer Center in Houston, where he is also Chief, Section of Blood and Bone Marrow Transplantation. He is a fellow of the American College of Physicians, and a member of the American Society of Hematology, and the American Society for Clinical Oncology. Dr. Champlin was the first President of the Council of Donor Transplant and Collection Centers of the National Marrow Donor Program, appointed Chairman, Bone Marrow Transplant Committee of the National Cancer Center Network in 1995 and serves as Chairman of the Scientific

Affairs Committee of the American Society of Blood and Marrow Transplantation.

Dr. Champlin has been associated with the International Bone Marrow Transplant Registry (IBMTR) for many years and serves on the IBMTR's Executive Committee and Scientific Advisory Committee. He also serves on the Executive Committee and Scientific Advisory Committee of the Autologous Blood and Marrow Transplant Registry (ABMTR).

An international expert in leukemia and bone marrow transplantation, he is Chair of the IBMTR's Histocompatibility, Alternative Donors, and Stem Cell Sources Working Committee and co-chair of the Chronic Lymphocytic Leukemia Working Committee, a joint scientific committee of the IBMTR and ABMTR.

IBMTR CELEBRATES SILVER ANNIVERSARY

In its 25th year of existence as a productive scientific organization, the International Bone Marrow Transplant Registry (IBMTR) took time out on September 13th for its silver Anniversary Celebration, "Sharing Knowledge - Sharing Hope." Commemorative events included a scientific symposium at the Medical College of Wisconsin attended by more than 200 members of the Milwaukee area transplant and oncology community, Registry founders, Executive and Advisory Committee members, and international representatives from many participating teams.

Speakers included Irving Weissman (Stanford University School of Medicine, Palo Alto, California) speaking on the biology of the hematopoietic stem cell, Mary Horowitz (Medical College of Wisconsin, Milwaukee) speaking on alternative stem cell sources, Malcolm Brenner (St. Jude's Children's Research Hospital, Memphis, Tennessee) speaking on gene therapy, and Megan Sykes (Harvard Medical School, Boston, Massachusetts) speaking on xenotransplantation. Perspectives on the history of the IBMTR and the field of transplantation and a vision for the future were shared by three of the Registry's founding members, Dr. Robert Good of All Children's Hospital, St. Petersburg, Florida; Professor Georges Mathé of the Institut de Cancerologie et d'Immunologie, Villejuif, France; and Dr. George W. Santos of The John Hopkins University School of Medicine, Baltimore, Maryland.

The symposium was followed by a spectacular gala dinner at the Milwaukee Art Museum on Saturday evening, attended by almost 300 Registry friends and supporters. A video presentation, sponsored and produced by Rockwell Automation Allen-Bradley Company of Milwaukee, a founding supporter of the Registry, provided a moving perspective on the Registry's history, and the importance of its work to patients. Dan Rutz, Managing Editor for CNN Health and Medical News, and Mrs. Sue Ann Thompson, First Lady of the State of Wisconsin and a cancer survivor, gave thought-provoking commentaries on cancer care.

Most importantly, the program honored the thousands of transplant recipients and their families. They have, by participating in clinical research and sharing their information with the medical community, played the most important role in the progress made over the past 25 years. Some of these patients were present to share in the Anniversary Dinner. Others had their stories told through a photograph display developed by local artists and premiered at the event. This exhibit will be displayed throughout Southeast Wisconsin and at international scientific meetings.

Our heartfelt thanks go out to the many sponsors and supporters whose generosity and participation made the 25th Anniversary Celebration of the IBMTR a memorable occasion and to all whose contributions have made the past 25 years of scientific work possible.

The International Bone Marrow Transplant Registry (IBMTR) celebrated its 25th anniversary September 13, 1997 with an educational symposium, featuring nationally and internationally known cancer researchers, followed by a gala dinner.

(Photo) Mary M. Horowitz, MD, MS, Scientific Director of the IBMTR, poses with IBMTR founders: (left to right) Robert L. Truitt, PhD, Professor of Pediatrics, Medical College of Wisconsin; George W. Santos, MD, The Johns Hopkins University School of Medicine, Baltimore, MD; Prof. Georges Mathé, Institut de Cancerologie et d'Immunologie, Paris; Robert A. Good, MD, PhD, All Children's Hospital, St. Petersburg, FL; and Robert Peter Gale, MD, PhD, chair of the IBMTR Scientific Advisory Committee and Bone Marrow and Stem Cell Transplant Director, Salick Health Care, Los Angeles.

IBMTR Founder: Alfred A. Rimm, PhD

An article in our 25th Anniversary Newsletter reviewed the history of the IBMTR and ABMTR. However, in my column I amazingly (and embarrassingly) failed to cite contributions of one of the Registry's founders: Alfred A. Rimm. In retrospect I understand why: Al was such a central figure in the IBMTR/ABMTR for so long he became part of the Registry's identity. Mort Bortin never considered Al a "founder"; he *was* the Registry.

Al entered the bone marrow transplant world as Mort's statistical collaborator in murine transplant studies. Their early studies dealt with issues like radiation chimeras, graft-vs-host disease, graft-vs-leukemia and the like. Re-reading these articles today, I am amazed how the central issues Mort and Al raised are the focus of current research. I am also reluctant to try to quantify progress in understanding some issues Mort and Al identified in 1970 (I am referring to substance rather than techniques).

Al volunteered to help Mort with statistical analyses of the early ACS/NIH Bone Marrow Transplant Registry. He also helped bring Mort and his collaborators from Mount Sinai Hospital in Milwaukee to the Medical College of Wisconsin (the current site of the Statistical Center). The first IBMTR/ABMTR-related publication I found by Al is from 1972 making this year the 25th anniversary of Al's involvement with us. This publication was followed by almost 75 more in which Al and his colleagues provided statistical support for IBMTR/ABMTR analyses.

Al's contributions to our organization are too numerous to list. I am especially grateful for three: (1) introducing us to new, innovative techniques for statistical analyses, (2) input to our grant submissions, and (3) recruiting Mary Horowitz. Statisticians are, on average (or perhaps modally), odd. But not Al: doesn't everyone survive weeks on champagne and apples? And I suppose most folks have 4-sided reversible Scotch plaid ties (something to do with kabalah?).

Al left the Medical College of Wisconsin in 1993 to head the Department of Epidemiology and Biostatistics at Case Western Reserve University. Their gain is our loss.

-- Robert Peter Gale, MD, PhD
IBMTR Scientific Advisory
Committee Chair

FOUNDATION AND CORPORATE SUPPORT OF THE IBMTR / ABMTR

By **Susan Ladwig, MA** **Associate Director of Development, Statistical Center**

All of us at the IBMTR/ABMTR Statistical Center thank the many contributors who have joined our international collaboration for research in blood and marrow transplantation. Private support for the Registries continues to be vitally important since federal grants cover only 60 percent of the Statistical Center's budget. We gratefully acknowledge the support of the Medical College of Wisconsin; the National Cancer Institute; the National Institute of Allergy and Infectious Disease; the National Heart, Lung and Blood Institute; the Department of Defense; and the generosity of the following foundations and corporations:

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Several corporations have joined the IBMTR/ABMTR Corporate Membership Program (see above). The annual membership program provides member organizations with informational materials on blood and bone marrow transplantation developed by the IBMTR/ABMTR Information Resource Service.

The program includes subscriptions to the *Statistical Center Report on Survival Statistics for Blood and Marrow Transplants, IBMTR and ABMTR Newsletters*, the worldwide *IBMTR/ABMTR Directory of Blood and Marrow Transplant Teams*, and the *IBMTR/ABMTR Summary Slides on State-of-the-Art in Blood and Marrow Transplantation* as well as invitations to our meetings and educational forums and access to the IBMTR/ABMTR databases for simple analyses. These resources are useful for marketing managers, medical directors, research directors, product managers, case managers or transplant coordinators.

For additional information on the Corporate Membership Program, please contact Susan Ladwig, Associate Director of Development ☎ (414) 456-8363, Fax: (414) 456-6530.
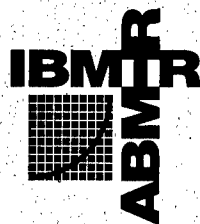
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International Bone Marrow Transplant Registry
Autologous Blood & Marrow Transplant Registry

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Blood and Marrow Transplants
A Basic Introduction

1. What is bone marrow?

Bone marrow is a substance found in the hollow bones of the hips, legs and arms. Special cells in the bone marrow called "stem cells" or "hematopoietic stem cells" produce all circulating blood cells including red cells which carry oxygen, white cells which make up the body's immune system and platelets which prevent bleeding.

2. Why are transplants needed?

Some people have diseases that alter or destroy the bone marrow. Others have diseases that can only be cured with high doses of radiation and drugs (sometimes called high-dose chemotherapy.) These high-dose treatments kill cancer cells but also kill normal bone marrow stem cells. Once the stem cells are destroyed. blood production stops. Blood or bone marrow transplants restore stem cells destroyed by disease or treatment.

3. What is the difference between bone marrow and blood stem cell transplants?

All transplants supply hematopoietic stem cells to restore blood production. When the stem cells are collected directly from bone marrow, the transplant is called a bone marrow transplant. When the stem cells are collected from the blood, the tranplant is called a blood stem cell transplant or a peripheral blood stem cell transplant.

4. What is the difference an allogeneic and an autologous transplant?

Allogeneic transplants use blood or bone marrow cells from another person, usually a sibling but sometimes another relative or an unrelated donor. Autologous transplants use the patient's own blood or bone marrow cells which are removed prior to high-dose therapy. frozen and later returned.

Frequently Asked Questions

1. How many transplants are done and for what indications?

There is no central repository registering ALL blood and marrow transplants. However. using data from worldwide surveys of transplant activity and data we collect here at the IBMTR/ABMTR. we periodically estimate the number of blood and marrow transplants performed worldwide and in North America. See 1998 Summary Slides for these figures (1 and 7).

2. Where is the best place to go for a transplant?

There is no one answer to this question. The decision about where to have a transplant done depends on many factors: geographic proximity and accessibility, experience of the center with a particular disease or type of transplant, a patient's comfort with the expertise and the personality of the treating physicians and the facility, requirements of particular insurance plans and others. Some resources for information that might help in this decision are listed below.

The **National Marrow Donor Program (NMDP)** has a directory of participating transplant centers that describes each center. summarizes its areas of expertise and provides contact information. It also gives some center-specific outcome information.

The **Oncology Nursing Society** has a directory called, "Bone Marrow Transplant Nursing Resource Directory". In this directory they list U.S. transplant centers by state and give limited details such as: how many transplants were performed for 1996, contact names and numbers, and how long the program has been opened. Please note. all transplant centers are not listed in this directory. They survey all institutions and only include those who respond to their survey. The Oncology Nursing Society can be reached at **412-921-7373** or visit their website at www.ons.org.

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The **BMT Newsletter** has an issue entitled, "Choosing a BMT Center." This issue provides insight into what to look for in a transplant center.

BMT LINK is another source for information on choosing a transplant center. They have a pamphlet. "A Survivors Guide to a Transplant". There is a section which deals with choosing a center. It lists questions which might help one decide on where to go for a transplant.

3. I would like information about a particular disease.

A patient's most important resource for information is his or her physician. There is no substitute for a open and frank conversation with one's doctor. We encourage patients to talk to their physicians frequently and to seek clarification on confusing issues. Before acting on information obtained through this or other websites, the information should be discussed with a physician familiar with the patient's medical situation.

All IBMTR/ABMTR publications are available upon request. Please check our Publication List.

The IBMTR/ABMTR December 1998 Newsletter includes figures on outcomes of transplants for the most common indications.

The **BMT Newsletter** also highlights specific diseases in many of its issues.

____ is a website produced by the IBMTR/ABMTR, the National Marrow Donor Program and the American Society for Blood and Marrow Transplantation. It includes articles written by transplant experts at both basic and technical levels.

4. How can I request specific information from the IBMTR/ABMTR database?

This information is most appropriate for physicians and clinical investigators making treatment decisions or planning clinical studies. Please fill out the IBMTR/ABMTR Information Request Form.

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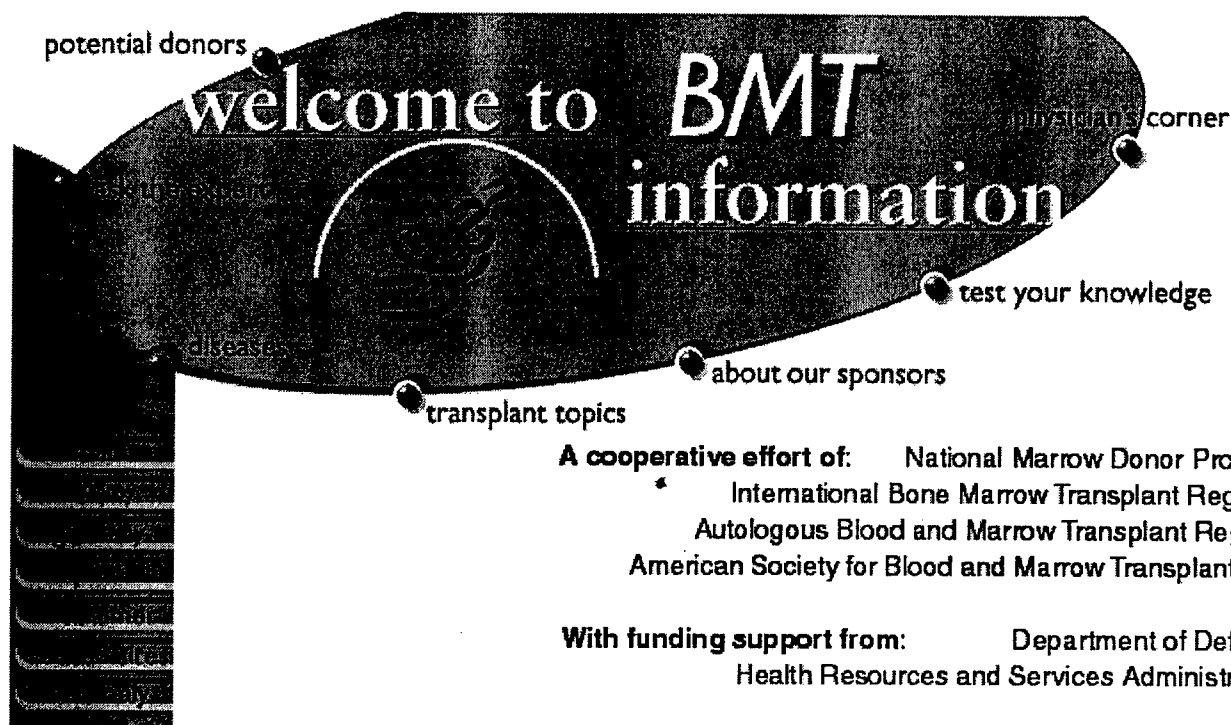
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Autologous Blood and Bone Marrow Transplantation for Breast Cancer

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Assistant Scientific Director, IBMTR/ABMTR

Mary Horowitz, M.D., M.S.
Scientific Director, IBMTR/ABMTR

Introduction | Current Data | Clinical Trials | Published Papers

Introduction

Basic | Technical

Breast cancer is the second most common cause of cancer deaths in North America. The American Cancer Society estimates that more than 180,000 new cases of breast cancer were diagnosed in 1996 (1). Fortunately, many women are cured of their disease through surgery with or without radiation therapy, chemotherapy, or hormone treatments after surgery. Unfortunately, the disease returns in many women, either at the same or another site. Still other women have metastasis—disease outside the breast and lymph nodes—at the time of diagnosis, which cannot be cured with surgery. So, scientists continue to look for effective treatments for women with recurrent or high-risk breast cancer.

A treatment used currently for women with recurrent breast cancer is high-dose chemotherapy followed by transplantation of the patient's own bone marrow or blood cells. This is called autologous transplant or *autotransplant*. This treatment, however, is controversial for patients with breast cancer. The therapy is expensive, and there is little information comparing the results of autotransplant with the results of standard chemotherapy. This controversy about autotransplants has caused legal problems between patients wishing to have the treatment and insurance companies refusing to pay for this treatment.

In response to the controversy, the U.S. Congress asked the General Accounting Office to write a report about the treatment. This report is entitled "Coverage of Autologous Bone Marrow Transplantation for Breast Cancer" (2). The report analyzed the financial and political issues that affect the use of new technologies for health care in the United States. But this report did not reach any conclusions about the use of autotransplants for patients with breast cancer.

The National Cancer Institute is trying to compare the results of autotransplants with those of standard therapy by sponsoring several large clinical trials in cancer centers throughout the United States. In these trials, patients are randomly assigned to different types of treatment and their outcomes are compared. Patients enrolling in these trials have a 50-50 chance of receiving a transplant. Randomized trials are the best way to determine whether one treatment is better than another. These trials are especially appropriate in evaluating treatments such as autotransplants for breast cancer, in which the true benefit is unknown. Several studies show that patients treated in clinical trials have better outcomes than those treated outside of trials, regardless of which treatment they receive. However, many patients and their physicians hesitate to get involved in these trials because they do not want to be assigned to the standard therapy (3).

Despite the controversy, the use of autotransplants for patients with breast cancer has greatly increased in the past 6 years. Data reported to the Autologous Blood and Marrow Transplant Registry (ABMTR) show that about 3,500 autotransplants were done in 1995 for patients with breast cancer.

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Current Data

Background

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High-dose chemotherapy combined with autotransplant is being used more and more often to treat breast cancer in women who have a high risk of their breast cancer continuing or recurring. Two organizations keeping track of information about transplants for breast cancer and other diseases are the International Bone Marrow Transplant Registry (IBMTR) and the Autologous Blood and Marrow Transplant Registry (ABMTR) of North America. According to data from these organizations, breast cancer is now the most common reason for blood cell or bone marrow transplantation.

Currently, most reports published about autotransplants include only a few patients and do not compare results with standard chemotherapy. Only one small study has been published of women with metastatic breast cancer treated with either standard dose or high-dose chemotherapy (1). This study included only women with newly diagnosed metastatic breast cancer. It showed a longer survival period for patients who had autotransplants. However, the results of larger trials and other clinical studies are not yet available. Until these results are published, most questions about the advantages of autotransplant cannot be answered. In the meantime, data about the safety of autotransplants and the outcome of patients having this treatment are available from the ABMTR and other sources.

What Is the ABMTR?

The Autologous Blood and Marrow Transplant Registry (ABMTR) of North America is an organization of more than 200 transplant institutions in the United States, Canada, and Central and South America. These institutions report data about autotransplants to a Statistical Center at the Medical College of Wisconsin. The ABMTR began to collect data in 1992. About half of the autotransplants done in North America for patients with all diseases are registered with the ABMTR (2,3). (Click here for a list of participating centers.)

Trends in Autotransplants and Deaths for Patients with Breast Cancer

From 1989 to 1995, the number of autotransplants increased by almost six times. At first, autotransplants were done primarily for patients with metastatic disease. More recently, autotransplants

have been done more often for women with primary breast cancer (stage II, stage III, and inflammatory disease). Most important, the percentage of patients who had died by 100 days after treatment decreased from 18% (1989) to 5% (1995).

Outcome for Patients with High-Risk Primary Breast Cancer

Figure 1 shows the estimates of survival time after autotransplant in patients with stage II, stage III, and inflammatory breast cancer. The chances that a woman with stage II breast cancer will still be living 3 years after autotransplant are about 75%. For women with stage III breast cancer, the chance is 70%. For those with inflammatory breast cancer, the chance is about 50%.

For a woman with stage II breast cancer, the chance that she will still be living *and her disease will not have progressed* 3 years after autotransplant is about 65%. For women with stage III breast cancer, this chance is 60%. For those with inflammatory breast cancer, the chance is 40%. In 1995, only 4% of patients undergoing autotransplant had died by 100 days after treatment.

Outcome for Patients with Metastatic Breast Cancer

A patient's survival after autotransplant for metastatic breast cancer is often predicted by how the disease responds to standard dose chemotherapy before the patient has the transplant (Fig. 1, Fig. 2). The way that breast cancer responds to standard dose therapy is classified in one of three ways: 1) complete disappearance, 2) partial disappearance (in which the size of disease is reduced by at least half), or 3) resistant. For a woman whose metastatic cancer disappears completely after standard chemotherapy, the chance that she will still be alive 3 years after having an autotransplant is about 45%. For women with only partial disappearance after standard dose chemotherapy, the chance of surviving 3 years after autotransplant is about 30%. For those with resistant metastatic cancer, the chance of surviving 3 years is about 15%.

For a woman whose metastatic cancer disappears completely after standard chemotherapy, the chance that she will still be living *and her disease will not have progressed* 3 years after autotransplant is about 30%. For women with partial disappearance, this chance is about 15%. For those with resistant metastatic breast cancer, this chance is about 5%. In 1995, 6% of patients with metastatic breast cancer who underwent autotransplant died by 100 days after treatment.

Autotransplants Versus Standard Dose Therapy for Patients with Breast Cancer

Scientists are not certain whether the results reported for patients undergoing autotransplant are better than those reported for patients having standard dose therapy. Currently, comparing the results of these two treatments can cause several problems. A bias in the selection of patients for study may occur. This bias can happen because patients planning to have an autotransplant often undergo extensive medical tests before the procedure. These tests can detect hidden diseases and exclude from the study any patients who might have poor results (4). In addition, patients who undergo autotransplants are often chosen because their lungs, heart and kidneys are functioning well. These factors are likely to lead to better results.

If scientists are to compare the results of autotransplant and standard dose therapy in a useful way, they must analyze the data and carefully adjust it for factors that affect the patient, the disease, and the transplant. The best way to do this is in large randomized trials in which all patients are evaluated and followed carefully, regardless of the therapy they are assigned. Several studies suggest that people treated in randomized trials have better outcomes than people receiving the same treatment outside of trials.

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Captions

Fig. 1. The probability of survival after autotransplant for patients with breast cancer, 1989-1995.

Fig. 2. The probability of survival after autotransplant for patients with metastatic breast cancer based on the sensitivity of the disease to standard chemotherapy before transplant, 1989-1995.

Links to other resources of use to physicians and other health professionals caring for patients with breast cancer.

A comprehensive information service is provided by the NIH PDQ Search Service at http://cancernet.nci.nih.gov/trials/pdq_search.html

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Clinical Trials

Basic | Technical

A *randomized clinical trial* (or Phase III trial) is an experiment done on human beings to evaluate the results of two or more therapies. Patients participating in the trials are randomly assigned to one of the therapies being studied. The outcomes of the patients receiving each type of treatment are then analyzed and compared.

Trial:
Comparison of high-dose chemotherapy and autotransplant versus standard dose chemotherapy in women with stage II and IIIA breast cancer and at least ten positive axillary nodes (NCI Clinical Trial #CLB-9082 INT-0163)

Description:
This Phase III trial is sponsored by the National Cancer Institute. The trial will compare the results of two groups of women undergoing treatment for stage II or IIIA breast cancer who have at least ten positive axillary nodes. The two treatments are:
1. High-dose chemotherapy with autotransplant and radiotherapy of the chest wall

2. Standard dose chemotherapy and radiotherapy of the chest wall after initial chemotherapy

Purposes:

To compare the survival rates of women with stage II or IIIA breast cancer who undergo these two treatments

To compare the toxic effects of these two treatments

Trial:

Randomized study of adjuvant chemotherapy versus adjuvant chemotherapy followed by high-dose chemotherapy and autotransplant in women with stage II or III breast cancer at high risk of recurrence (NCI Clinical Trial #EST-2190 INT-0121)

Description:

This Phase III trial is sponsored by the National Cancer Institute. The trial will compare the results of two types of treatment for women with stage II or stage III breast cancer who are at high risk of recurrence. The two treatments are:
1. Adjuvant chemotherapy
2. Adjuvant chemotherapy followed by high-dose chemotherapy and autotransplant

Purposes:

To compare the sites and rates of recurrent cancer, the survival rates, and toxicity of these two treatments in women with stage II or III breast cancer and ten or more positive lymph nodes

To evaluate the rate and degree of contamination of bone marrow by breast cancer cells at the time patients enter the study and after they undergo chemotherapy

To document the changes in psychosocial function in patients during treatment and compare their recovery of this function after treatment

To establish a bank of tumor samples for future laboratory study

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Trial:

Comparison of conventional chemotherapy versus high-dose chemotherapy and autotransplant in women with metastatic breast cancer whose disease responds to conventional chemotherapy (NCI Clinical Trial #E-PBT01 NCI-T90-0180D)

Description:

This Phase III trial is sponsored by the National Cancer Institute. It will compare the results of two treatments in women with metastatic breast cancer whose disease responds to conventional chemotherapy. The two treatments are:
1. Conventional chemotherapy
2. High-dose chemotherapy and autotransplant

Purposes:

To compare the survival rates of patients with metastatic breast cancer whose disease responds to conventional chemotherapy and who undergo these two treatments

To compare the financial costs and toxicity of these two treatments

To evaluate the patients' quality of life associated with these two treatments

---

Trial:

Randomized study of autologous transplant versus transplantation of peripheral blood stem cells

in patients with high-risk breast carcinoma (NCI Clinical Trial #FHCRC-772.1 NCI-H94-0370)

Description:

This Phase III trial is sponsored by the National Cancer Institute. The trial will determine which source of blood cells grafts faster in patients with high-risk or advanced breast cancer. The two sources of cells are:

1. Autologous bone marrow
2. Peripheral blood stem cells stimulated with granulocyte colony-stimulating factor (G-CSF)

Purposes:

To determine which of these two sources of stem cells leads to a faster graft in patients with high-risk or advanced breast cancer who are given G-CSF after undergoing transplant

To compare the rate and duration of infection, requirements for transfusion, the length of hospital stay, and the rate of complications between patients in these two groups

To compare the total cost of hospitalization between these two groups of patients

To evaluate long-term engraftment in the two treatment groups

To evaluate hidden tumor cells in peripheral blood and bone marrow, and to evaluate T-cell populations in collections of peripheral blood stem cells

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Trial:

Randomized study of high-dose chemotherapy versus conventional chemotherapy followed by chemotherapy combined with autotransplant in women with primary breast cancer involving four to nine axillary nodes (NCI Clinical Trial #S-9623 SWOG-9623)

Description:

This Phase III trial is sponsored by the National Cancer Institute. It will compare the results of two treatments in women with primary breast cancer involving four to nine lymph nodes. The two treatments are:

1. Intensive sequential doses of three types of chemotherapy
2. Conventional chemotherapy followed by chemotherapy combined with autotransplant

Purposes:

To compare survival rates between women undergoing these two treatments

To compare the toxic effects associated with these treatments

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Autologous Blood and Bone Marrow Transplantation for Breast Cancer

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Introduction

Basic | **Technical**

Breast cancer is the second most common cause of cancer deaths in North America, and the American
Cancer Society estimates that more than 180,000 new cases of breast cancer were diagnosed in 1996 ([1]).
Many women with breast cancer are cured after local surgery with or without radiotherapy. Many others,
however, have a recurrence of disease (either locally or at distant sites) after primary surgery or present
with metastatic disease at diagnosis. Therefore, better treatments for patients with high-risk primary and
advanced breast cancer continue to be investigated.

The role of high-dose chemotherapy with autologous hematopoietic stem cell support (autotransplant) as
treatment for breast cancer remains controversial. The rationale for autotransplants is the dose-response
relationship between many chemotherapy drugs and breast cancer, suggesting that increasing doses
beyond the limits of bone marrow toxicity may increase cures. The controversy results from the high
cost of autotransplants and the paucity of data comparing outcome with standard dose therapy. There
have been legal disputes between patients wishing to undergo the procedure and third-party payers
refusing to reimburse the costs. Some of these disputes have received extensive exposure.

Responding to the controversy, the U.S. Congress commissioned the General Accounting Office (GAO)
to review this area. Its findings are summarized in a report entitled "Coverage of Autologous Bone
Marrow Transplantation for Breast Cancer" ([2]). The GAO report made some recommendations about the
financial and political issues governing dissemination of new technologies and health care in the United
States. It produced no conclusions regarding use of autotransplants for patients with breast cancer. To
determine the relative efficacy of autotransplants and standard therapy, several large trials sponsored by
the National Cancer Institute are being conducted by the U.S. cooperative oncology groups. Accrual of
patients into these trials is slower than expected, however, because patients and physicians are reluctant
to accept randomization to standard dose therapy. A careful review of the continued relevance and
necessity of these trials was recently published ([3]).

Despite the controversy, use of autotransplants for patients with breast cancer has increased dramatically
over the past 6 years. According to data reported to the Autologous Blood and Marrow Transplant
Registry (ABMTR), which receives information on 40% to 50% of all transplants done in North
America, about 3,500 autotransplants were done in 1995 for patients with breast cancer, making this
disease the single most common indication for blood or marrow transplant of any kind (autologous or

allogeneic).

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Current Data on Autotransplants for Patients with Breast Cancer

Basic | **Technical**

Background

High-dose chemotherapy (either with or without radiation therapy) with autologous hematopoietic stem cell support (autotransplant) is increasingly used to treat breast cancer. According to data reported to the International Bone Marrow Transplant Registry (IBMTR) and the Autologous Blood and Marrow Transplant Registry (ABMTR) of North America, breast cancer is now the most common indication for hemopoietic stem cell transplant of any kind, either autologous or allogeneic. Published reports of autotransplants include relatively few patients, and substantial reporting biases are likely to exist (see selected list of references). Only one randomized study has been published. This study included 90 women with newly diagnosed metastatic breast cancer treated with either standard dose therapy or two courses of high-dose chemotherapy with stem cell support (1). This study showed a statistically significant advantage in both survival and disease-free survival for patients receiving autotransplants versus those receiving conventional dose chemotherapy. However, the 3-year survival in the autotransplant group was only 20%, suggesting that few women are cured with this approach. The study has been criticized because of its small sample size and choice of regimens. Until results of larger randomized trials or other carefully controlled clinical studies are available, most questions regarding the comparative efficacy of autotransplant versus standard dose therapy will remain unanswered. However, considerable data are available from the ABMTR and other sources regarding the safety and outcomes of high-dose treatment.

What Is the ABMTR?

The Autologous Blood and Marrow Transplant Registry of North America (ABMTR) is a voluntary organization of more than 200 transplant centers in the United States, Canada, and Central and South America. ABMTR centers report data on consecutive autotransplants to a Statistical Center at the Medical College of Wisconsin. The Statistical Center also collects data for allogeneic blood and bone marrow transplants (allotransplants) from centers participating in the International Bone Marrow Transplant Registry (IBMTR), a similar but independent organization of allotransplant centers worldwide. The ABMTR began collecting data in 1992. Data were collected retrospectively for patients receiving autotransplants between 1989 and 1992, and prospectively thereafter. Based on data collected by the Center for Disease Control Hospital Surveys (2,3), about half of autotransplants done in North America for all diseases are registered with the ABMTR. (Click here for a list of participating centers.)

Trends in Autotransplants and Mortality for Patients with Breast Cancer

Table 1 lists data reported to the ABMTR on almost 7,000 women receiving autotransplants for breast cancer. The number of autotransplants increased almost sixfold from 1989 to 1995. The disease stage at the time of transplant also changed significantly: while most autotransplants in 1989 were for metastatic disease, now more than half are done as adjuvant therapy for primary breast cancer (stages II, III and inflammatory disease). Stem cells collected from the blood are now the most common form of hematopoietic support. Most importantly, 100-day mortality decreased significantly from 18% in 1989-90 to 5% in 1995.

Table 1. Trends in autotransplants for breast cancer reported to the ABMTR 1989-1995.

Outcome in High-Risk Primary Breast Cancer

Kaplan-Meier estimates of survival after autotransplants for stages II, III and inflammatory breast cancer are shown in Figure 1. Three-year probabilities of survival after autotransplant are about 75% for women with stage II, 70% for women with stage III, and about 50% (range 40%-64%) for women with inflammatory breast cancer. Three-year probabilities of progression-free survival after autotransplant are about 65% for women with stage II, 60% for women with stage III, and 40% for women with inflammatory breast cancer. In 1995, the 100-day mortality rate was 4%.

Outcome in Metastatic Breast Cancer

Survival after autotransplant for metastatic breast cancer is predominantly determined by the responsiveness of the disease to standard dose therapy before transplant. Response is usually categorized as complete (disappearance of all known disease for 4 or more weeks), partial (a 50% or greater reduction in the size of measurable disease), or resistant (any response less than partial). Figures 1 and 2 show Kaplan-Meier estimates of survival after autotransplant for women with metastatic breast cancer according to disease-responsiveness before transplant. Three-year probabilities of survival after autotransplant are about 45% for women with complete response, 30% for women with partial response, and 15% for women with resistant metastatic breast cancer. Three-year probabilities of progression-free survival after autotransplant are about 30% for women with complete response, 15% for women with partial response and 5% for women with resistant metastatic breast cancer. In 1995, the 100-day mortality rate was 6%.

Autotransplants Versus Standard Dose Therapy for Breast Cancer

It is uncertain whether the results above are superior to those obtained in similar women using standard dose therapy. Comparing historical results with conventional therapy has caused several problems. Selection biases may occur since patients considered for autotransplant often have extensive medical evaluations before the procedure. This may detect occult metastatic disease in women with primary breast cancer and exclude from adjuvant transplant trials those patients who are likely to have poorer outcomes (4). Additionally, autotransplants are often restricted to women with good performance status and near-normal pulmonary, cardiac and renal function. Conversely, results of autotransplants might be expected to be worse compared to standard dose therapy when patients are treated as part of phase I studies with experimental and potentially toxic protocols. Meaningful comparisons of autotransplant versus standard dose therapy require careful adjustment for differences in factors related to the patient, the disease, and transplant, ideally in large randomized clinical trials.

References

1. Bezwoda WR, Seymour L, Dansey RD: High-dose chemotherapy with hematopoietic rescue as primary treatment for metastatic breast cancer: A randomized trial. Journal of Clinical Oncology 13:2483-2489, 1995.
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2. National Hospital Discharge Survey for 1990 and 1991. U.S. Department of Health and Human Services, Public Health Service, Center for Disease Control. National Center for Health Statistics. Hospital Care Statistics Branch, 6525 Belcrest Road, Hyattsville, MD, 20782.

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3. Graves EJ: Detailed diagnoses and procedures, National Hospital Discharge Survey, 1989. Vital and Health Statistics - Series 13: Data from the National Health Survey. 108:1-236, 1991.
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4. Crump M, Goss PE, Prince M, Girouard C: Outcome of extensive evaluation before adjuvant therapy in women with breast cancer and 10 or more positive axillary lymph nodes. Journal of Clinical Oncology 14:66-69, 1996.
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Captions

Fig. 1. Probability of survival after autotransplants for breast cancer, 1989-1995.

Fig. 2. Probability of survival after autotransplants for metastatic breast cancer according to pretransplant chemosensitivity, 1989-1995.

Links to other resources of use to physicians and other health professionals caring for patients with breast cancer.

A comprehensive information service is provided by the NIH PDQ Search Service at http://cancernet.nci.nih.gov/trials/pdq_search.html

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Clinical Trials

Basic | **Technical**

For details about enrolling a patient in one of these trials, contact the Chairpersons listed at the end of each trial summary. The details listed are correct as of the date given at the end of the title.

Additional Phase I and II trials are listed with the PDQ search service and are also conducted at individual transplant institutions.

<div align="center">

Trials

</div>

- CLB-9082 INT-0163
- EST-2190 INT-0121
- E-PBT01 NCI-T90-0180D
- FHCRC-772.1 NCI-H94-0370
- S-9623 SWOG-9623

CLB-9082 INT-0163

NCI HIGH PRIORITY CLINICAL TRIAL --- Phase III Randomized Comparison of High-Dose Chemotherapy with Autologous Marrow and Peripheral Stem Cell Support vs Standard-Dose Chemotherapy Following Adjuvant Chemotherapy in Women with Stage II/IIIA Breast Cancer with at Least 10 Positive Axillary Nodes (Summary Last Modified 09/96)
STATUS: Active AGE RANGE: over 18

NCI-sponsored, NCI cooperative group program

OBJECTIVES:
I. Compare disease-free and overall survival of women with stage II/IIIA breast cancer randomized to

receive high-dose cyclophosphamide/cisplatin/carmustine with autologous bone marrow/peripheral stem cell support plus chest wall irradiation vs. conventional doses of the same drugs plus chest wall irradiation, administered after 4 courses of adjuvant cyclophosphamide/doxorubicin/fluorouracil (CAF).

II. Compare the toxic effects of these 2 regimens.

PROTOCOL ENTRY CRITERIA:

--Disease Characteristics--

Histologically confirmed adenocarcinoma of the breast

Pathologically confirmed stage IIA, IIB, or IIIA (i.e., T1-3, N1-2, M0)

10-or more positive axillary nodes required

Absence of distant metastases, evidenced by:
    Negative bone scan
    Negative bilateral bone marrow aspirate/biopsy
    Negative CT of head, chest, abdomen, pelvis

Hormone receptor status:
    Any estrogen receptor (ER) or progesterone receptor (PR) status accepted, including unknown
    Knowledge of ER and PR status desired

No bilateral breast cancer

--Prior/Concurrent Therapy--

Biologic therapy:
    Not specified

Chemotherapy:
    No prior chemotherapy

Endocrine therapy:
    Not specified

Radiotherapy:
    No prior radiotherapy

Surgery:
    Radical or modified radical mastectomy or lumpectomy with level I/II axillary dissection required
    Preferably within 2 weeks prior to initiating cyclophosphamide/doxorubicin/fluorouracil (CAF)
    Not more than 8 weeks prior to initiating CAF (10 weeks with permission of the study chairman)
    Negative resection margins required
    Lymphatic and vascular involvement permitted

--Patient Characteristics--

Age:
    Over 18
    No upper limit, but over physiologic 50 expected to tolerate treatment less well

Sex:
    Women only
Menopausal status:

Pre-, post-, or perimenopausal

Performance status:
    CALGB 0 or 1
    Karnofsky 80%-100%

Hematopoietic:
    ANC at least 1,800/mL
    Platelets at least 100,000/mL
    Hemoglobin greater than 10 g/dL
    Bone marrow cellularity at least 30%

Hepatic:
    Bilirubin not more than 1.5 times normal
    AST not more than 1.5 times normal

Renal:
    Creatinine less than 1.8 mg/dL
    BUN not more than 1.5 times normal

Cardiovascular:
    Left ventricular ejection fraction (LVEF) on MUGA at least 45% at rest and at least 5% increase
    with exercise (exercise test not required if LVEF is at least 55%)
    EKG required within 90 days prior to entry
    No uncontrolled or significant cardiovascular disease, i.e.:
        No myocardial infarction within 1 year
        No congestive heart failure

Pulmonary:
    FVC at least 60% of predicted
    FEV1 at least 60% of predicted
    DLCO at least 60% of predicted

Other:
    No previous or concomitant second malignancy except:
        Curatively treated cervical cancer
        Nonmelanomatous skin cancer

Negative viral titers, e.g.:
    HIV
    HBsAg
    Hepatitis C

No serious medical/psychiatric condition that would:
    Preclude protocol therapy
    Prevent informed consent

Companion quality-of-life study (CLB-9066) must be offered

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EST-2190 INT-0121

NCI HIGH PRIORITY CLINICAL TRIAL --- Phase III Randomized Study of Adjuvant CAF (Cyclophosphamide/Doxorubicin/Fluorouracil) vs Adjuvant CAF Followed by Intensification with High-Dose Cyclophosphamide/Thiotepa plus Autologous Stem Cell Rescue in Women with Stage I/III Breast cancer at High Risk of Recurrence (Summary Last Modified 02/96)
STATUS: Active AGE RANGE: 15 to 60

SPONSORSHIP
NCI-sponsored, NCI cooperative group program

OBJECTIVES:
I. Compare sites and rates of recurrence, disease-free survival, overall survival, and toxicity of adjuvant chemotherapy with CAF (cyclophosphamide, doxorubicin, fluorouracil) vs. adjuvant CAF followed by marrow ablation with cyclophosphamide/thiotepa and autologous stem cell rescue in women with stage II/III breast cancer and 10 or more positive lymph nodes.

II. Evaluate prospectively the incidence and degree of occult marrow contamination with breast cancer cells at the time of study entry and following CAF chemotherapy by analyzing samples of marrow using a panel of monoclonal antibodies specific for breast cancer.

III. Document the changes in psychosocial function that occur during treatment on either regimen, and compare post-treatment recovery of psychosocial function.

IV. Establish a bank of paraffin-embedded tumor samples for future laboratory study.

PROTOCOL ENTRY CRITERIA:

--Disease Characteristics--

Biopsy-proven epithelial carcinoma of the breast with at least 10 involved lymph nodes

Stage II/III disease
>   Synchronous bilateral breast cancer eligible provided primaries occurred within 6 weeks of each
>   other
>   Contralateral intraductal cancer eligible

The following conditions exclude:
>   T4 disease
>   Apocrine, adenoidcystic, or squamous carcinoma
>   Inflammatory carcinoma of the breast
>   Lesions fixed to skin or chest wall
>   Peau d'orange skin changes
> • Asynchronous bilateral infiltrating breast cancer

Radical or modified radical mastectomy or breast-sparing surgery with axillary dissection required
within 12 weeks of entry
>   Negative surgical margins required
>   Type of procedure, number of nodes examined, number of positive nodes, and tumor size must be
>   reported
>   Breast-sparing surgery must have included wide excision (i.e., removal of gross tumor plus normal
>   breast tissue)

Bone marrow aspirate, bilateral core biopsy, and bone scan must be negative for tumor
>   Aspiration and biopsy not required for patients who received 1 or 2 courses of any
>   doxorubicin-based chemotherapy prior to entry

Hormone receptor status:
>   Estrogen and progesterone receptor status must be determined by either biochemical or
>   immunohistochemical assays

--Prior/Concurrent Therapy--

Biologic therapy:
>   No prior therapy with colony-stimulating factors for breast cancer

Chemotherapy:
>   1 or 2 prior courses of any doxorubicin-based chemotherapy allowed provided documentation of
>   treatment is available

Endocrine therapy:
>   No prior hormonal therapy for breast cancer except up to 21 days of tamoxifen that is stopped
>   prior to entry
>   Prior postmenopausal estrogen therapy allowed but must be discontinued prior to entry

Radiotherapy:
>   No prior radiotherapy
>   Postoperative radiotherapy required on study

Surgery:
>   Surgery completed no more than 12 weeks prior to entry
>>   Surgery completed no more than 12 weeks prior to start of chemotherapy in patients who
>>   receive one or two courses of doxorubicin-based chemotherapy prior to randomization

--Patient Characteristics--

Age:
    15 to 60

Sex:
    Women only

Menopausal status:
    Pre- or postmenopausal

Performance status:
    ECOG 0 or 1

Hematopoietic:
    (obtained within 2 weeks prior to entry)
    WBC at least 4,000/mL
    Platelets at least 100,000/mL

Hepatic:
    (obtained within 2 weeks prior to entry)
    Bilirubin no more than 1.2 times normal
    AST (or ALT) no more than 1.2 times normal
    Alkaline phosphatase no more than 1.2 times normal

Renal:
    Not specified

Cardiovascular:
    Left ventricular ejection fraction (by MUGA) at least 50% or equal to or greater than the lower
    limit of institutional normal
    No prior angina pectoris requiring nitrate therapy
    No myocardial infarction within 6 months
    No uncontrolled congestive heart failure
    No uncontrolled hypertension
    No major ventricular arrhythmia

Pulmonary:
    FEV1 at least 60% of predicted
    DLCO (corrected) at least 60% of predicted
    Lung volume at least 60%
    Lung volume not required if uncorrected FEV1 and DLCO greater than 80%
    No symptomatic obstructive or restrictive lung disease

Other:
    No symptomatic CNS disease of any etiology
    No insulin-dependent diabetes mellitus
    No uncompensated major thyroid dysfunction
    No uncompensated major adrenal dysfunction
    No HIV positivity
    No prior malignancy within 5 years except:
       In situ breast cancer (lobular or ductal)
       Inactive nonmelanomatous skin cancer
       In situ cervical cancer
    No pregnant or nursing women
    Assessment of insurance coverage required

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E-PBT01 NCI-T90-0180D

NCI HIGH PRIORITY CLINICAL TRIAL --- Phase III Randomized Comparison of Conventional CMF Maintenance vs High-Dose Combination Chemotherapy plus Autologous Bone Marrow and Peripheral Stem Cell Rescue in Women with Metastatic Breast Cancer Responding to Conventional Induction Chemotherapy (Summary Last Modified 06/96)
STATUS: Active AGE RANGE: 18 to 60

NCI-sponsored, NCI cooperative group program

OBJECTIVES
I. Compare time to failure and overall survival of patients with metastatic breast cancer responding after 4-6 courses of conventional induction chemotherapy who are randomly assigned to 24 months of conventional maintenance chemotherapy with CMF (cyclophosphamide/methotrexate/fluorouracil) vs. high-dose chemotherapy with cyclophosphamide/thiotepa/carboplatin followed by autologous bone marrow and peripheral stem cell rescue.

II. Compare the toxicity of these 2 regimens.

III. Compare the financial costs of these 2 regimens.

IV. Evaluate the quality of life associated with these 2 treatments.

PROTOCOL ENTRY CRITERIA

--Disease Characteristics--

Histologically documented adenocarcinoma of the breast

Metastatic or recurrent disease

No leptomeningeal or brain metastases
Inflammatory breast cancer requires distant metastases
Adequate hepatic function (see below) required with liver metastases
Metastases to ipsilateral regional lymph nodes (supraclavicular or cervical) only may be treated by mastectomy or locoregional radiotherapy

Hormonal receptor status:
Estrogen receptor (ER)-negative or unknown
ER-positive (at least 10 fmol/mg cytosol protein) bone/soft tissue disease eligible only if progressed on at least 1 hormone manipulation in the adjuvant or metastatic setting
ER-positive, visceral disease eligible without prior hormone therapy

Bidimensionally measurable or evaluable disease, as follows:
Not irradiated or progressed since radiotherapy

Evaluable disease defined as:
Blastic and mixed blastic/lytic lesions with no anticipated need for palliative radiotherapy during first 3 courses
Pure osteolytic lesions
Positive bone scan as only evidence of metastasis permitted provided patient has analgesic requirement or decreased performance status
    Evidence must be unequivocal if bone x-ray is negative
Hepatic metastases greater than 2 cm on CT or MRI or of any size if biopsy-proven
Abdominal or pelvic mass on CT or MRI
Multinodular or confluent lung or skin metastases
Cytologically positive pleural effusion

No large third-space fluid accumulation that cannot be drained

No large pericardial effusion

--Prior/Concurrent Therapy--

Biologic therapy:
Not specified

Chemotherapy:
One course of induction therapy as specified in the protocol allowed prior to entry
No other chemotherapy for metastatic disease, except patient may have relapsed after primary treatment for stage IV disease by virtue of metastasis only to ipsilateral supraclavicular nodes
At least 6 months between adjuvant chemotherapy and recurrence

Endocrine therapy:
Prior hormone manipulation required for bone or visceral metastasis unless rapidly progressing

At least 4 weeks since or no benefit from oophorectomy for metastatic or recurrent disease

Radiotherapy:
None to pelvic bones or lower spine
No anticipated requirement for palliation during first 3 courses

Surgery:
At least 2 weeks since major surgery

--Patient Characteristics--

Age:

18 to 60

Sex:
    Women only

Menopausal status:
    Premenopausal or postmenopausal

Performance status:
    ECOG 0 or 1

Hematopoietic:
    ANC at least 1,500/mL
    Platelets at least 100,000/mL

Hepatic:
    Bilirubin not greater than 2.0 mg/dL
    AST/alkaline phosphatase not greater than 2 times normal
    If liver function compromised by metastatic disease:
        Bilirubin not greater than 5.0 mg/dL
        AST not greater than 600 U/mL

Renal:
    After hydration:
        Creatinine not greater than 1.5 mg/dL and/or
        Creatinine clearance at least 60 mL/min

Cardiovascular:
    No significant cardiovascular disease, i.e.:
        No congestive heart failure
        No myocardial infarction within 3 months
        No arrhythmia requiring medication
        No poorly controlled hypertension (diastolic over 100 mm Hg)

Pulmonary:
    No significant non-neoplastic pulmonary disease

Other:
    No active infection
    No active peptic ulcer disease
    No brittle insulin-dependent diabetes mellitus
    No hospitalization for psychiatric illness, including severe depression or psychosis
    No current alcohol or drug abuse
    No pregnant or nursing women
    Not HIV seropositive and no clinical evidence of AIDS
    No active second malignancy within 10 years except:
        Curatively treated nonmelanomatous skin cancer
        In situ cervical carcinoma

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FHCRC-772.1 NCI-H94-0370

Phase III Randomized Study of Autologous Bone Marrow vs G-CSF-Stimulated Peripheral Blood Stem Cell Transplantation for High-Risk Breast Carcinoma (Summary Last Modified 06/94)
STATUS: Active AGE RANGE: no greater than 65

SPONSORSHIP
NCI-sponsored, NCI grant supported

OBJECTIVES
I. Determine which stem cell source, autologous bone marrow (AuBM) or autologous peripheral blood stem cells (PBSC) mobilized with granulocyte colony-stimulating factor (G-CSF), results in more rapid engraftment in patients with high-risk or advanced breast carcinoma given post-transplant G-CSF.

II. Compare the rate and duration of infection, transfusion requirements, days of hospitalization, and rate of transplant-related complications between patients receiving PBSC vs. AuBM.

III. Compare the total cost of hospitalization when using PBSC vs. AuBM.

IV. Evaluate long-term engraftment in the two treatment groups.

V. Evaluate occult tumor cells in peripheral blood and marrow, and evaluate T-cell populations in PBSC collections.

PROTOCOL ENTRY CRITERIA

--Disease Characteristics--

High-risk breast carcinoma that has failed conventional therapy or has a greater than 50% chance for

relapse, i.e.:
>   Stage II with more than 10 positive nodes
>   Stage III
>   Stage IV

No evidence of marrow involvement on biopsy
>   Marrow positive only by immunocytochemistry allowed

>   No rapidly progressing disease requiring immediate therapy

>   No carcinomatous meningitis or untreated CNS disease

>   Hormone receptor status:
>   Not specified

--Prior/Concurrent Therapy--

>   Biologic therapy:
>   Not specified

>   Chemotherapy:
>   No more than 3 prior courses of myelosuppressive chemotherapy for metastatic disease

>   Endocrine therapy:
>   Not specified

>   Radiotherapy:
>   No prior pelvic irradiation

>   Surgery:
>   Not specified

--Patient Characteristics--

>   Age:
>   No greater than 65

>   Menopausal status:
>   Not specified

>   Sex:
>   Not specified

>   Performance status:
>   Karnofsky 70%-100%

>   Hematopoietic:
>   ANC at least 1,500/mL
>   Platelets at least 150,000/mL
>   Marrow cellularity at least 60% of normal
>   No history of prolonged neutropenia (ANC below 500 for more than 30 days) after
>   conventional-dose chemotherapy

>   Hepatic:
>   Bilirubin no greater than 1.5 mg/dL

>   Renal:

Creatinine no greater than 1.5 mg/dL
No history of severe cyclophosphamide-induced hemorrhagic cystitis

Cardiovascular:
LVEF at least 45%

Other:
No HIV antibody
Willing to undergo multiple aphereses
Marrow available or patient willing to undergo marrow harvest

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S-9623 SWOG-9623

Phase III Randomized Study of Intensive Sequential Doxorubicin, Paclitaxel, and Cyclophosphamide vs Doxorubicin/Cyclophosphamide Followed by STAMP I or STAMP V Combination Chemotherapy with Autologous Stem Cell Rescue in Women with Primary Breast Cancer and 4-9 Involved Axillary Lymph Nodes (Summary Last Modified 08/96)
STATUS: Active AGE RANGE: adult

NCI-sponsored, NCI cooperative group program

OBJECTIVES
I. Compare disease-free and overall survival following intensive sequential chemotherapy with doxorubicin, paclitaxel, and cyclophosphamide versus standard dose doxorubicin/cyclophosphamide followed by high-dose STAMP I (cyclophosphamide/cisplatin/carmustine) or STAMP V (cyclophosphamide/carboplatin/thiotepa) and autologous peripheral blood progenitor cell or bone marrow rescue in women with operable breast cancer and 4-9 positive axillary lymph nodes.

II. Compare the toxic effects associated with these regimens.

PROTOCOL ENTRY CRITERIA

--Disease Characteristics--

Histologically confirmed adenocarcinoma of the breast with 4-9 histologically involved axillary lymph nodes
No known T4, N3, or M1 disease

Prior breast-sparing surgery or modified radical mastectomy plus axillary lymph node dissection required
Surgical margins negative for invasive or noninvasive ductal carcinoma
At least 10 nodes sampled
No more than 12 weeks since definitive surgery

Synchronous bilateral breast carcinoma eligible, provided:
  One breast meets the eligibility criteria
  Other breast has fewer than 10 involved nodes and is not N3 or T4

Hormone receptor status:
  Not specified

--Prior/Concurrent Therapy--

Biologic therapy:
  Not specified

Chemotherapy:
  No prior chemotherapy

Endocrine therapy:
  Not specified

Radiotherapy:
  No prior radiotherapy to the breast

Surgery:
  See Disease Characteristics

--Patient Characteristics--

Age:
  Adult

Sex:
  Women only

Menopausal status:
  Any status

Performance status:
  SWOG 0 or 1

Hematopoietic:
  WBC at least 3,000/mL
  ANC at least 1,000/mL
  Platelets at least 100,000/mL

Hepatic:
  Bilirubin no greater than 1.5 times normal
  AST no greater than 1.5 times normal

Renal:
  Creatinine clearance at least 60 mL/min

Cardiovascular:
  Left ventricular ejection fraction at rest at least 45% by MUGA
  EKG abnormalities require patient clearance by cardiologist
  No uncontrolled or significant cardiac disease
  No congestive heart failure
  No second- or third-degree heart block or other serious cardiac conduction abnormality
  No atrial or ventricular arrhythmia

No requirement for medication known to affect cardiac conduction unless:
    Given for reasons other than heart failure or arrhythmia
    Patient cleared by a cardiologist

Pulmonary:
    FVC and FEV1 at least 60% of predicted
    DLCO at least 60%

Other:
    No HIV antibody
    Known HBsAg and hepatitis C status required
    No serious medical or psychiatric illness that precludes informed consent or study participation
    No second malignancy within 5 years except adequately treated:
        Nonmelanomatous skin cancer
        In situ cervical cancer
    No pregnant or nursing women
    Effective contraception required of fertile women

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Welcome to BMTInformation at www.bmtinfo.org

Selected list of recently published literature on autotransplants for patients with breast cancer by topics

Issues have been raised by the numerous published studies of small series of patients treated with autotransplants for breast cancer. Recently published data (authors, title and journal) are listed below according to topic.

A. Conditioning regimens used for autotransplant in women with Primary Breast Cancer
B. Conditioning regimens used for autotransplant in women with Recurrent or Metastatic Breast Cancer
C. Radiation therapy following autotransplant.
D. Immune modulation posttransplant to induce antitumor activity.
E. Detection of residual tumor cells in the stem cell source.
F. Purging of stem cell source to remove residual breast cancer cells.
G. Toxicity of autotransplants for breast cancer.
H. Safety of autotransplants for breast cancer.
I. Legal and financial issues.
J. Randomized trials involving autotransplants for breast cancer.
K. Prognostic factors in autotransplants for metastatic breast cancer.
L. Double (Tandem) autotransplants for breast cancer.
M. Pharmacokinetic monitoring in autotransplants for breast cancer.
N. Quality of life after autotransplants for breast cancer.
O. Hemopoetic stem cell sources for autotransplants for breast cancer.
P. Autotransplants as outpatients.
Q. Change in disease stage with extensive evaluation

A. Conditioning regimens used for autotransplant in women with Primary Breast Cancer

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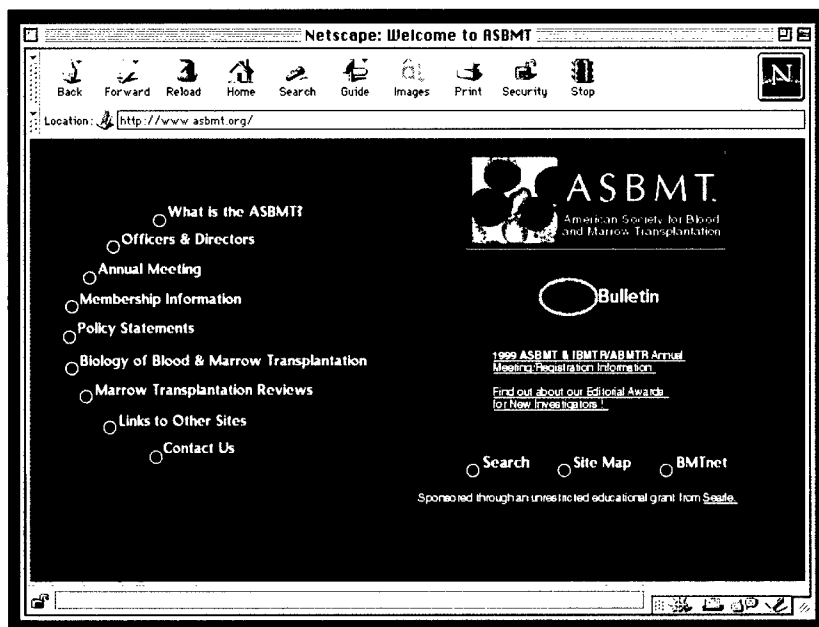American Society for Blood
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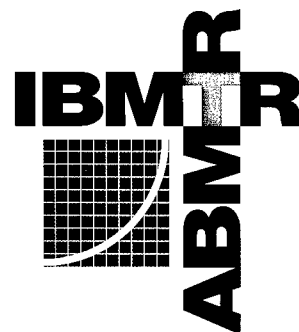
ASBMT

American Society for Blood and Marrow Transplantation

The web site at www.asbmt.org advances the mission of ASBMT — to represent and serve blood and marrow transplantation investigators, clinicians and the patients they care for.

Features of the web site include:

● ASBMT policy statements, including Guidelines for Clinical Centers and Guidelines for Training.

● Searchable full texts of articles in ASBMT periodicals, Biology of Blood and Marrow Transplantation and Marrow Transplantation Reviews.

● ASBMT officers and directors, including direct e-mail links.

● Investigator awards, editorial awards and other ASBMT programs and recognitions.

● ASBMT Annual Meeting program, registration and housing information.

● Membership application information.

● Links to other BMT sites, including medical and patient advocacy organizations and government agencies.

The web site will continue to evolve with new features and functions that serve the communications needs of ASBMT members.

ASBMT

The American Society for Blood and Marrow Transplantation is the leading individual membership organization promoting research, education and clinical practice in the field of blood and marrow transplantation.

ASBMT promotes high-quality BMT clinical care, clinical guidelines and standards, rapid advancement of the BMT field through basic and clinical research and an annual scientific meeting, scholarly publication through its Biology of Blood and Marrow Transplantation journal, effective representation of BMT to legislators and government regulators, representation of BMT interests to managed care and health plan administrators, and public and professional awareness and understanding of blood and marrow transplantation.

IBMTR/ABMTR

Sharing Knowledge. Sharing Hope.

The International Bone Marrow Transplant Registry (IBMTR) and the Autologous Blood and Marrow Transplantation Registry (ABMTR) are voluntary organizations of basic and clinical scientists collaborating in an effort to address important issues in blood and marrow transplantation. We are not a donor registry — we gather information on results of blood and marrow transplants. This information is used to guide clinical decisions and identify ways to improve transplant outcomes.

The IBMTR is an international study group engaged in ongoing investigation of allogeneic and syngeneic (identical twin) transplantation for more than 25 years. The ABMTR began collecting data from centers in North America and South America in 1991 on transplants using autologous bone marrow and/or blood cells.

The IBMTR/ABMTR Statistical Center is a division of the Health Policy Institute of the Medical College of Wisconsin in Milwaukee.

BMTnet

BMTnet is a cooperative effort among BMT organizations to coordinate web sites serving the blood and marrow transplantation field. BMTnet and its component web sites are supported by an unrestricted educational grant from Searle.

www.asbmt.org

Click on a calendar date for Annual Meeting program information.

Instant access to "Guidelines for Clinical Centers" and "Guidelines for Training."

Click on a state for a list of transplant centers.

Slide series illustrates trends in blood and marrow transplantation.

IBMTR/ABMTR

International Bone Marrow Transplant Registry/Autologous Blood and Marrow Transplant Registry

The web site at www.ibmtr.org serves the mission of IBMTR/ABMTR — to gather and disseminate information on results of blood and marrow transplants to aid clinical decisions and to identify ways to improve transplant outcomes.

Features of the web site include:

- Locations and contact information for transplant centers participating in the IBMTR/ABMTR.
- IBMTR/ABMTR studies in progress.
- Statistical summary slides, featuring data on the current status of blood and marrow transplantation.
- Full text of current and highlights of past IBMTR and ABMTR newsletters.
- IBMTR/ABMTR publications list.
- IBMTR and ABMTR Report Forms that can be printed directly from the web site.
- IBMTR/ABMTR Annual Meeting program, registration and housing information.
- Information on how to contact IBMTR/ABMTR Executive, Advisory and Working Committee members and the Statistical Center personnel, including many direct e-mail links.

New features and functions will be added, including Working Committee discussion rooms, on-line IBMTR/ABMTR registration forms, and other information service features, including disease-specific reports and survival data.

WHAT?

BMT information and resources on the Internet.

WHEN?

NOW.

This new web service is online, ready to serve you.

WHY?

To provide valuable information and reference materials, and to enhance communication among BMT clinicians, investigators and other health care professionals.

WHERE?

At: **www.bmtnet.org** — a comprehensive, central resource of blood and marrow transplantation topics.

www.asbmt.org — the new web site of the American Society for Blood and Marrow Transplantation (ASBMT)

www.ibmtr.org — the new web site of the International Bone Marrow Transplant Registry (IBMTR) and the Autologous Blood and Marrow Transplant Registry (ABMTR)

IBMTR/ABMTR Presentations on Breast Cancer at
National and International Meetings
1994-1998

November 1994

4th International Meeting of the Canadian Bone Marrow Transplant Group   Ottawa, Canada
P.A. Rowlings: BMT: What can we learn from the IBMTR/ABMTR database?

Chemotherapy Foundation Symposium XII   New York, USA
K. Fields: High dose chemotherapy with BMT in treatment of breast cancer

First International Cancer Congress   Hong Kong
K. Antman: High dose chemotherapy for breast cancer

January 1995

Second Symposium on Autotransplants   Keystone, USA
M.M. Horowitz: Overview of autologous transplantation

First Annual Meeting of the American Society for Blood & Marrow Transplantation   Keystone, USA
H. Sutton: Healthcare economics, reform and BMT
M.M. Horowitz: Outcomes assessment in BMT

February 1995

20th Annual Topics and Advances in Internal Medicine   San Diego, USA
R.E. Corringham: High dose chemotherapy in established breast cancer treatment

March 1995

High Dose Chemotherapy with Stem Cell Support for the Treatment of Breast Cancer   Bethesda, USA
M.M. Horowitz: Use of the ABMTR database

April 1995

Meeting of the United Network of Organ Sharing   New Orleans, USA
G.J. Elfenbein: Autologous BMT for breast cancer

May 1995

Future Directions in Stem Cell Transplantation   Teaneck, USA
M.M. Horowitz: Use of autologous and allogeneic marrow transplantation: An overview from the IBMTR

1

<div align="center">August 1995</div>

International Society for Experimental Hematology   Düsseldorf, Germany
P.A. Rowlings: Prognostic factors in autotransplants for metastatic breast cancer

<div align="center">September 1995</div>

6th Uruguayan Congress of Haematology   Montevideo, Uruguay
P.A. Rowlings: Autologous BMT, peripheral stem cells and their clinical applications

<div align="center">November 1995</div>

Columbian Society for Oncology   Cali, Columbia
W.P. Vaughan: Advances in autologous and allogeneic BMT

Meeting of the Ecuador National Cancer Institute   Quito, Ecuador
W.P. Vaughan: Advances in BMT

<div align="center">December 1995</div>

American Society of Hematology   Seattle, USA
P.A. Rowlings: Prognostic factors in autotransplants for metastatic breast cancer

<div align="center">January 1996</div>

1996 IBMTR/ABMTR Participants' Meeting   Keystone, USA
K. Antman: Autotransplants for breast cancer
J.O. Armitage: ABMTR update

Keystone Symposium on Blood Cell and Bone Marrow Transplants   Keystone, USA
M.M. Horowitz: Analyzing transplant outcomes: comparison with other therapies
J.O. Armitage: Do autotransplants uniquely cure cancer?
R.P. Gale: How do autotransplants cure cancer?
K. Antman: Breast cancer workshop

<div align="center">February 1996</div>

Blue Cross and Blue Shield Technology Center Forum   Chicago, USA
M.M. Horowitz: Outcomes of autologous transplants for breast cancer

Cancer Care for Non-Oncologists   Irvine, USA
R.O. Dillman: Biotherapy for cancer

Blue Cross and Blue Shield Technology Center Forum   Chicago, IL
M.M. Horowitz: High dose chemotherapy versus autotransplants for breast cancer and multiple myeloma

March 1996

California Society of Hospital Pharmacists   Newport Beach, USA
R.O. Dillman: New directions in stem cell transplants

4th International Symposium on Blood Cell Transplantation   Adelaide, South Australia
K.A. Antman: Blood cell transplants for breast cancer

Association of Cancer Executives   Philadelphia, USA
R.O. Dillman: Update on autologous BMT

22nd Annual Meeting of the European Group for Blood & Marrow Transplantation   Vienna, Austria
M.M. Horowitz: Challenges in using observational data to compare transplant and non-transplant treatment

April 1996

First South American Transplantation Meeting   Buenos Aires, Argentina
P.A. Rowlings: Autotransplant for metastatic breast cancer

4th International Symposium on Blood Cell Transplantation   Adelaide, South Australia
K.A. Antman: Blood cell transplants for breast cancer

Association of Cancer Executives   Philadelphia, USA
R.O. Dillman: Update on autologous BMT

May 1996

American Society of Clinical Oncology   Philadelphia, USA
J.K. Erban: Effect of legislation mandating coverage for BMT for breast cancer
H.M. Lazarus: Outcome of autotransplants in older adults

Experimental and Clinical Approaches in Oncology: Approaching the 21st Century   Teaneck, USA
M.M. Horowitz: Use of blood and marrow transplant in cancer treatment

Societat Catalana de Hematologia   Barcelona, Spain
A. Julia: Indications of transplantation

June 1996

Advances in Haematology   London, UK
M.M. Horowitz: Use of blood and marrow transplantation in cancer treatment

Indian Society of Hematology Meeting   Bombay, India
A.G. Mundia: Stem cell transplants in solid tumors

8th International Symposium on Autologous Marrow and Blood Transplantation   Arlington, USA
P.A. Rowlings: ABMTR results
P.A. Rowlings: Clinical studies in metastatic disease
D. Weisdorf: Comparison of unrelated donor BMT versus autologous BMT

Joint Statistical Meetings   Chicago, USA
J.P. Klein: Modeling multistate survival illustrated in bone marrow transplantation

September 1996

Meeting of the American Academy of Insurance Medicine   Kansas City, USA
M.M. Horowitz: Outcome of blood and marrow transplantation

October 1996

Oncology Nursing Conference 1996   Santo Domingo, Dominican Republic
C. Meneghetti: High dose chemotherapy and autologous BMT for breast cancer treatment

22nd Annual Meeting of the Brazilian Society of Hematology and Hemotherapy   Porto Alegre, Brazil
D.G. Tabak: BMT in the Mercosul - A Brazilian perspective

November 1996

Second Uruguayan Congress on BMT and PBSC Transplants   Montevideo, Uruguay
G. Milone: Advances in breast cancer treatment: BMT results

Conference of the Society of Blood Transfusion Hematology   Ho Chi Minh City, Vietnam
K.H. Lin: BMT in Taiwan

Meeting of the Polish Society of Hematology   Poznan, Poland
J. Hansz: Past, present and future of hematopoietic cell transplantation

March 1997

I Encontro sobre Transplante de Medula Ossea e Hemopatias Malignas   Curitiba, Brazil
S. Pavlovsky: The Argentine Group for Bone Marrow Transplantation experience
M.M. Horowitz: Chemotherapy vs. autologous vs. allogeneic BMT: Which is the best treatment?
M.M. Horowitz: Breast cancer - ABMTR data
A. Sumoza: BMT in Venezuela
K.A. Sobocinski: Analysis of transplant data

Annual Meetings of the BMT and Hematology Societies of Taiwan   Kaohseoug, Taiwan
C.H. Tzeng: An update on BMT and PBSCT

23rd Annual Meeting of the European Group for Blood and Marrow TransplantationAix-les-Bains, France
K. Antman: High-dose therapy for breast cancer in North America

German Stem Cell Meeting   Berlin, Germany
W. Hinterberger: Implications of posttransplant consolidative immunotherapy and immune modulation

1997 Blood Cell and Marrow Transplantation Multidisciplinary Symposium   Dallas, USA
P.A. Rowlings: Patient outcomes

April 1997

Canadian Apheresis Group Annual Meeting and Stem Cell Symposium   Quebec City, Canada
A. Keating: Overview of PBSC transplants

Brazilian College of Breast Surgeons   Rio de Janeiro, Brazil
D.G. Tabak: The role of BMT in the treatment of breast cancer

Bone Marrow Transplant Symposium   Graifswald, Germany
G. Dolken: High-dose chemotherapy as an adjuvant therapy for high-risk breast cancer

May 1997

Second National PBSCT Congress   Istanbul, Turkey
F. Arpaci: High-dose treatment in patients with solid tumors

American Society for Clinical Oncology   Denver, USA
M.M. Horowitz: Prognostic factors for outcome of autotransplants in women with high-risk breast cancer.

June 1997

VIII National Congress of the Italian Society of Hemapheresis   Trieste, Italy
A. Iacone: Background of Hemapheresis

August 1997

Aplastic Anemia Foundation of America International Patient Conference   Philadelphia, USA
M.M. Horowitz: Bone marrow transplant research and treatment in the United States and Europe

<div align="center">November 1997</div>

Dept. of Defense Breast Cancer Research Meeting   Washington, DC, USA
M.M. Horowitz: High-dose chemotherapy and blood or BMT for patients with high-risk breast cancer

Bone Marrow Transplantation for the Treatment of Autoimmune Disease   Worcester, USA
P.A. Rowlings: Standardized data collection for high-dose therapy and autologous stem cell transplants

<div align="center">January 1998</div>

1998 IBMTR/ABMTR Participants' Meeting   Keystone, USA
C. Bennett: Cost analysis of autologous stem cell transplants: preliminary results

<div align="center">March 1998</div>

Osaka Hematopoietic Stem Cell Transplantation Seminar   Osaka, Japan
M.M. Horowitz: Autologous transplantation: ABMTR results

60th Meeting of the Japanese Society of Hematology   Osaka, Japan
M.M. Horowitz: Increasing use of hematopoietic stem cell transplantation: IBMTR/ABMTR results

Kanto Bone Marrow Transplantation Seminar   Tokyo, Japan
M.M. Horowitz: Use of registry data in statistical analysis of bone marrow transplantation results

24th Annual Meeting of the European Group for Blood and Marrow Transplantation   Courmayeur, Italy
J.P. Klein: Comparing diseases and outcome measures: clinical and methodological problems

<div align="center">May 1998</div>

Transplantation in Hematology and Oncology   Münster, Germany
M.M. Horowitz: Status of blood and marrow transplantation

<div align="center">July 1998</div>

Ninth International Symposium on Autologous Blood and Marrow Transplantation   Dallas, USA
G.J. Elfenbein: Autotransplants for solid tumors
P.L. McCarthy: Autotransplants in men with breast cancer
R.L. Powles: Long term effects following autologous BMT: the London experience

<div align="center">September 1998</div>

Second Balkan International Congress of Oncology Meeting   Izmir, Turkey
F. Arpaci: High dose therapy: why and when
F. Arpaci: What is the best BMT strategy in patients with hematological malignancies and solid tumors?

8th Argentine Cancerology Congress & 5th Conference on Oncology Nursing   Buenos Aires, Argentina
G.J. Elfenbein: High dose therapy followed by autologous hematopoietic SCT for high risk breast cancer

AUTOTRANSPLANTS FOR BREAST CANCER
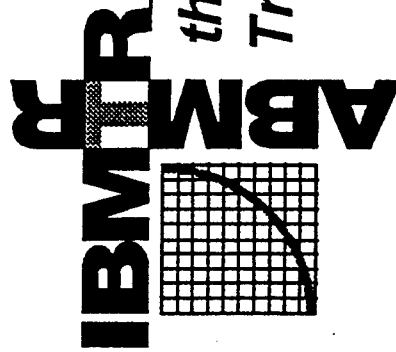
A Report from

the Autologous Blood and Marrow
Transplant Registry-North America

IBMTR
ABMTR

BREAST CANCER

- 180,000 new cases/year in U.S.

- 50% under age 65

- 20-25% "high-risk"
  (Stage II/III with ≥ 10 nodes; metastatic)

- > 20,000 potential autotransplant recipients
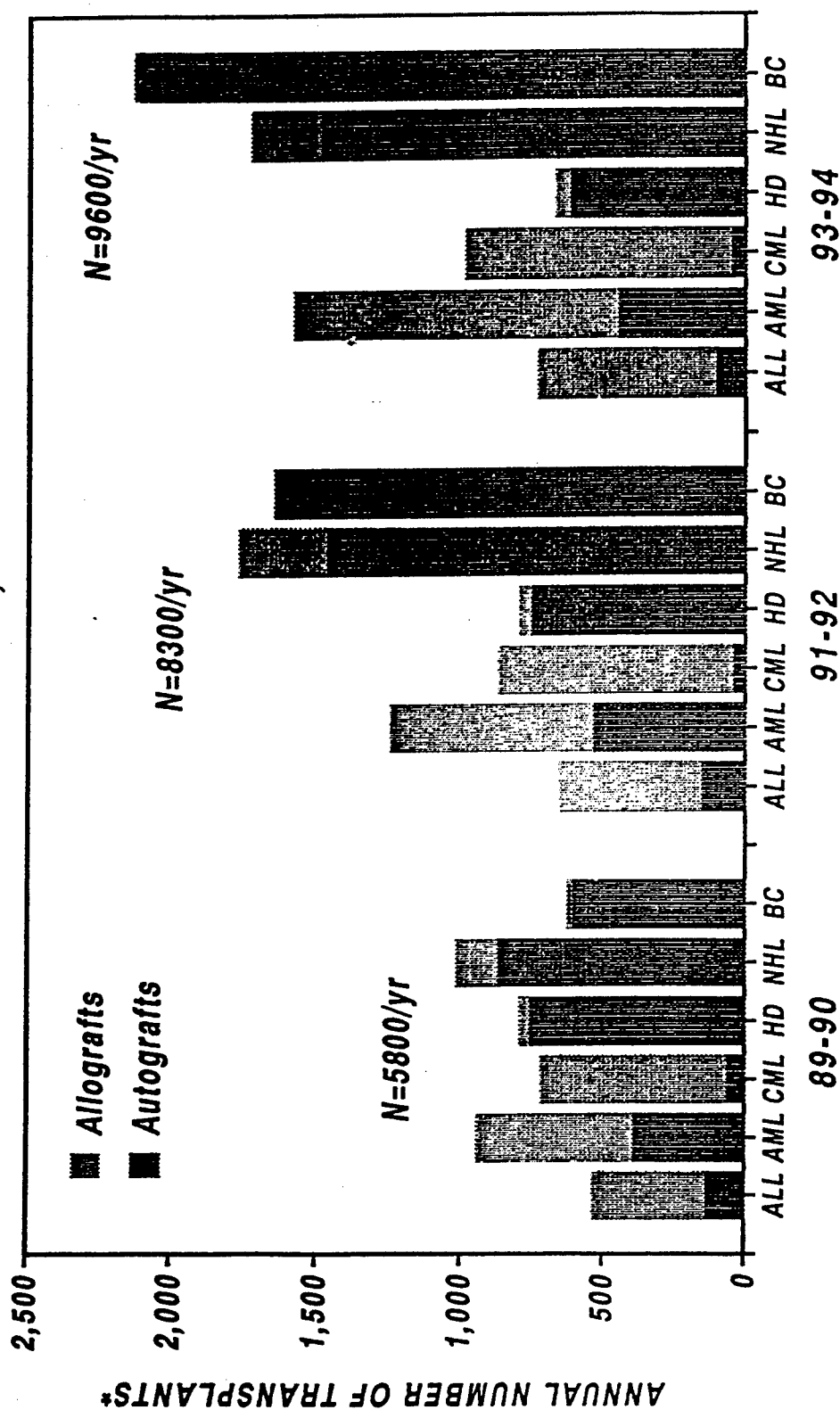
RATIONALE FOR AUTOTRANSPLANTS IN BREAST CANCER

- Experimental and clinical evidence for dose-response

- Dose limited by myelosuppression

INDICATIONS FOR BLOOD AND MARROW TRANSPLANTATION IN NORTH AMERICA 1995
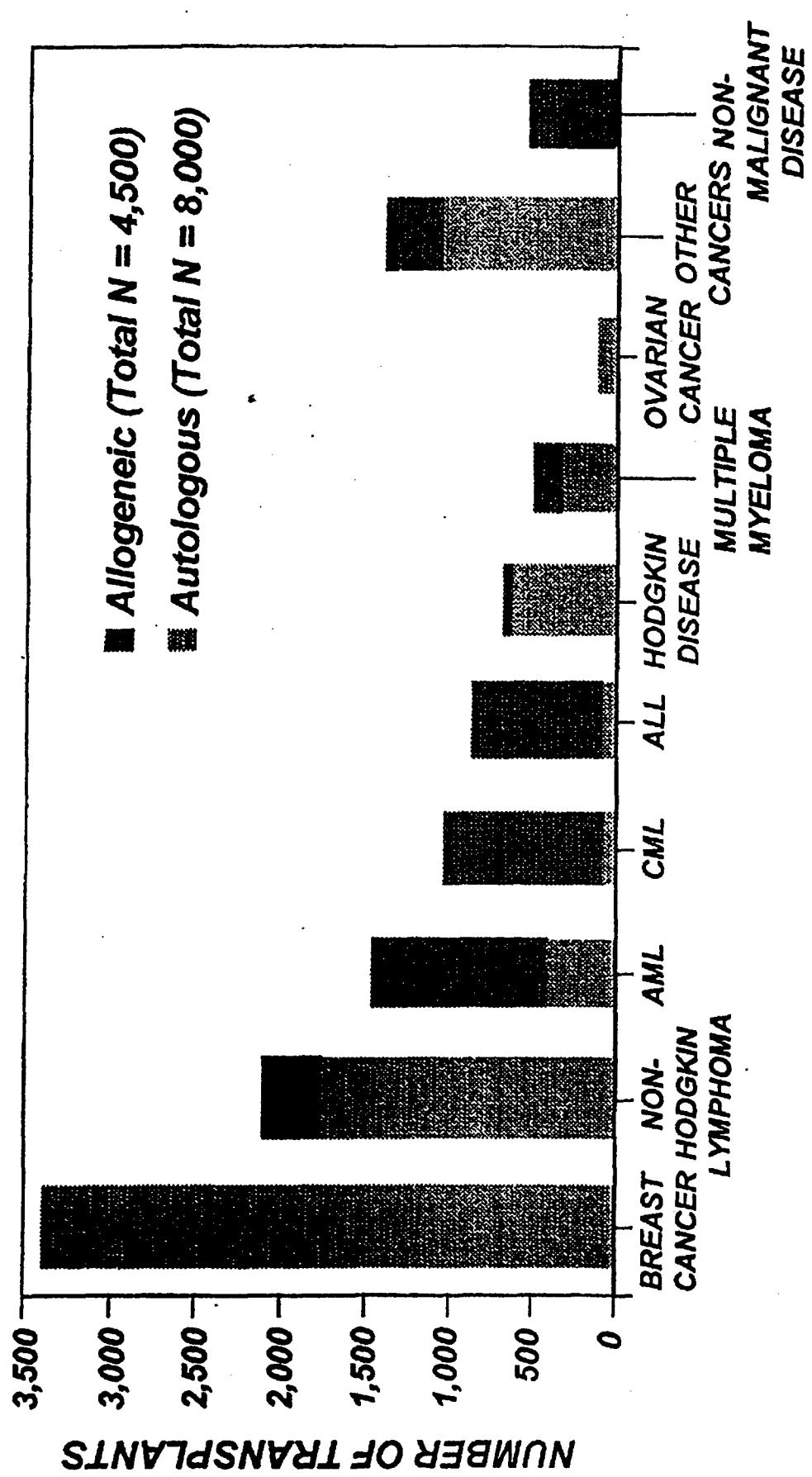
Overview of 5886 autotransplants for breast cancer performed between January 1989 and June 1995

ALLO- AND AUTOTRANSPLANTS
North America, 1989-94

KBC96 3

Allografts
Autografts

N=5800/yr

N=8300/yr

N=9600/yr

ALL AML CML HD NHL BC   ALL AML CML HD NHL BC   ALL AML CML HD NHL BC

89-90   91-92   93-94

*Average number of transplants done yearly in each 2-year period

ANNUAL NUMBER OF TRANSPLANTS*

2,500   2,000   1,500   1,000   500   0

AUTOTRANSPLANTS FOR BREAST CANCER

	1989	1990	1991	1992	1993	1994	Jan-June 1995
N	272	342	683	1069	1189	1513	818
Disease Stage at TX							
Local	7%	16%	23%	34%	31%	39%	49%
Metastatic	93%	83%	77%	65%	68%	50%	50%
Other	<1%	1%	<1%	1%	1%	1%	1%
Graph Type							
BM	81%	79%	58%	42%	30%	19%	10%
BM + PBSC	5%	7%	22%	33%	30%	25%	18%
PBSC	14%	14%	20%	25%	40%	56%	72%

ft - airway wonderful in slide

Other = patients with locally persistent or recurrent disease post conventional therapy

100-DAY MORTALITY AFTER AUTOTRANSPLANTS FOR BREAST CANCER

KBC96 5

PROGRESSION-FREE SURVIVAL AFTER AUTOTRANSPLANTS FOR PRIMARY (STAGE 2, 3 OR INFLAMMATORY) AND METASTATIC BREAST CANCER

KBC96 6

SURVIVAL AFTER AUTOTRANSPLANTS
FOR PRIMARY (STAGE 2, 3 OR INFLAMMATORY)
AND METASTATIC BREAST CANCER
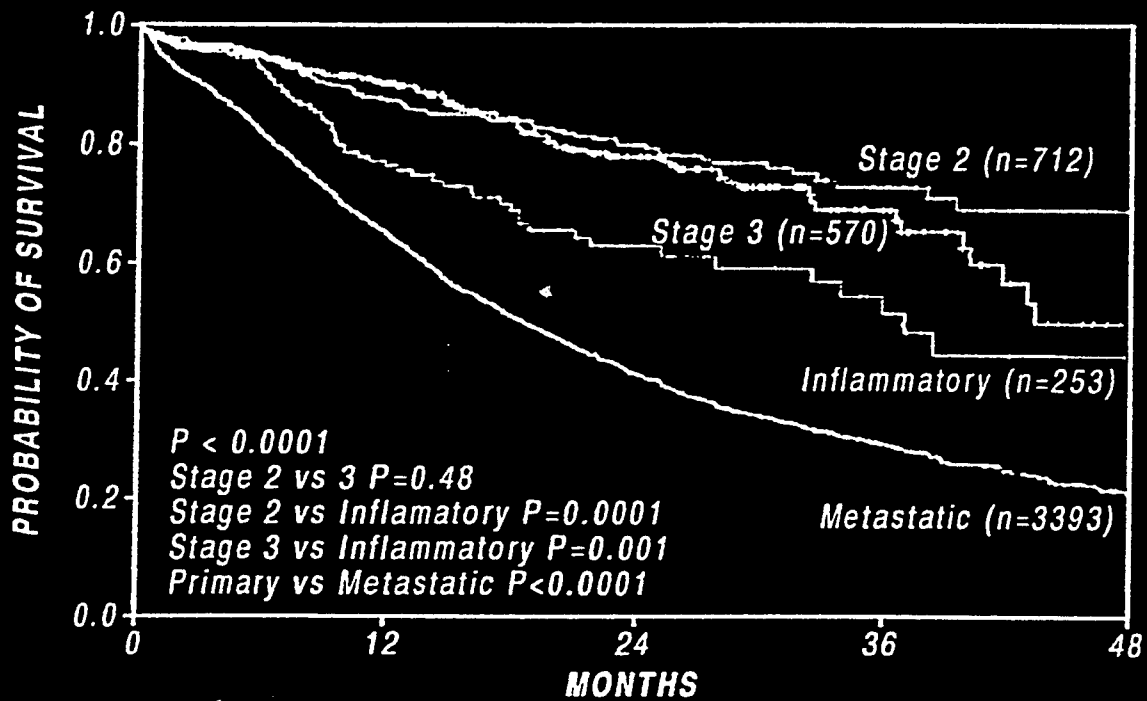
KBC96 7

PROGNOSTIC FACTORS IN AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER
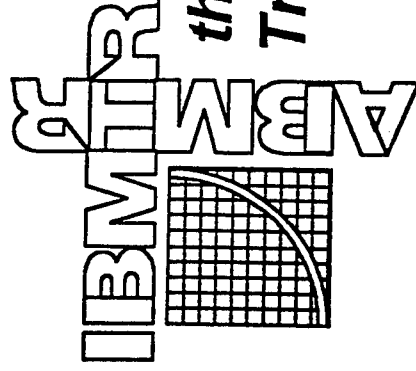
A Report from

the Autologous Blood and Marrow
Transplant Registry-North America

IBMTR
&
ABMTR

OBJECTIVES

- Determine outcome of autotransplants for metastatic breast cancer

- Identify patient-, disease- and transplant-related factors associated with higher progression-free survival

PATIENTS

- *1,188 women receiving autotransplants for metastatic breast cancer from 1989-95*

- *Reported to the ABMTR by 63 institutions in North and South America*

AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER
- Patient and Disease Characteristics -

N:		1,188
Median age (range):		44 (18-70)y
ER status:	Negative	33%
	Positive	59%
	Not Tested/borderline	8%
Stage at diagnosis:	Stage I	8%
	Stage II	32%
	Stage III	8%
	Not met, stage unknown	33%
	Metastatic	19%
Type of initial surgery:	Lumpectomy	17%
	Mastectomy	77%
	None	6%

AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER

- Prior Therapy -

Adjuvant chemotherapy:

19%	None
24%	CAF±other
31%	CMF±other
7%	Other
19%	Mets at diagnosis

Radiation therapy pretransplant: 52%

Hormonal therapy pretransplant: 51%

Anthracycline pretransplant: 83%

Total anthracycline dose: 240 (25-850) mg/m^2

Interval from dx to metastases: 21 (<1-238)m

19%	Mets at diagnosis
26%	≤ 18m
55%	> 18m

Interval from met. to transplant: 8 (<1-138)m

AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER
- Pretransplant Status -

Sites of disease:

63%	1-2 sites, not liver or CNS
11%	Liver ± other
2%	CNS±other
24%	3 or more sites

Response to chemotherapy:

23%	CR
33%	PR
29%	Resistant
15%	Undetermined

Karnofsky score pretransplant:

81%	90-100

AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER

- Transplant Characteristics -

Graft Source:

39%	BM
43%	Blood
18%	BM + Blood

Growth factors posttransplant: 76%

Year of transplant:

17%	1989-90
40%	1991-92
43%	1993-95

AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER

HIGH-DOSE CHEMOTHERAPY

N = 1,188

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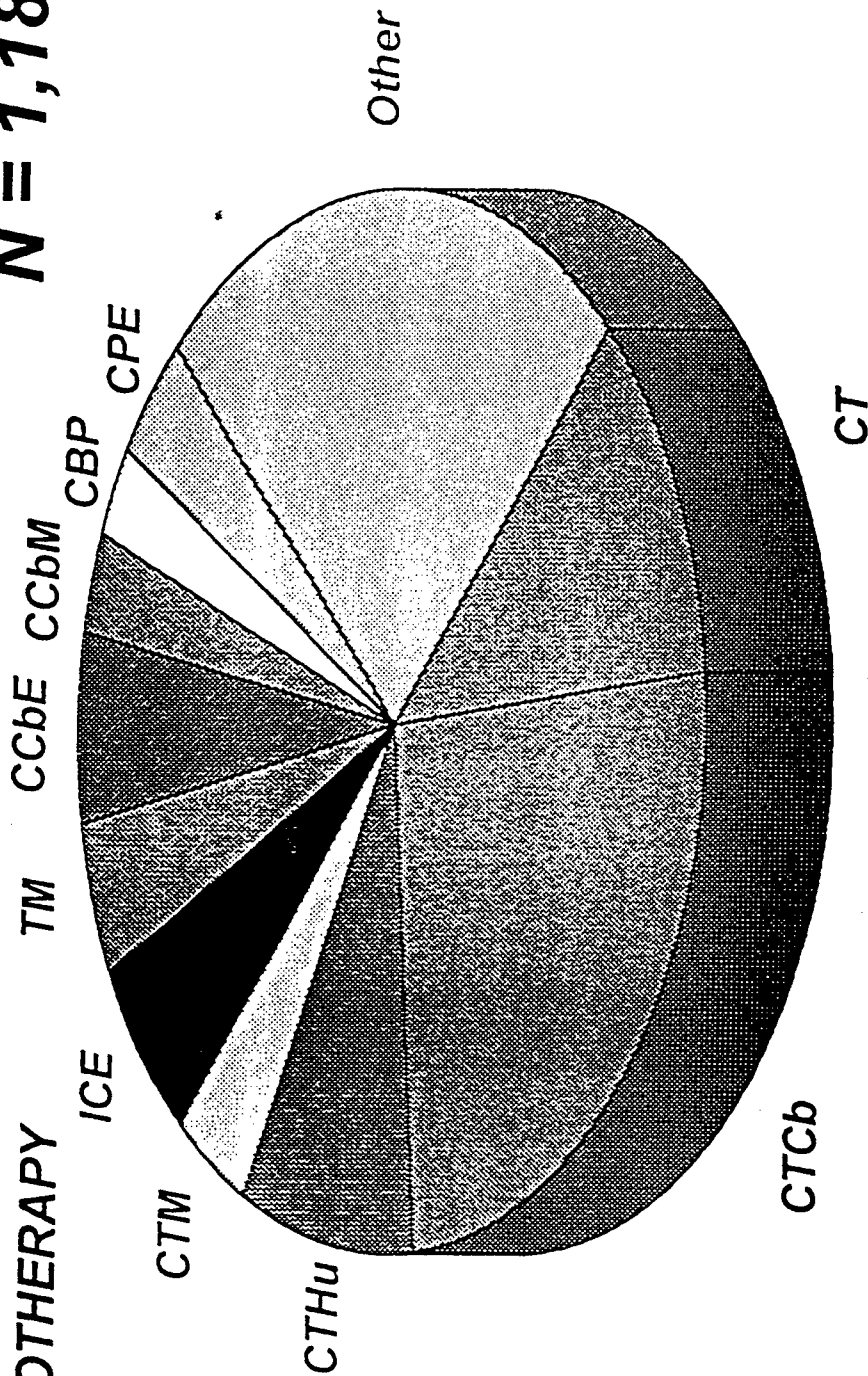
MULTIVARIATE ANALYSIS I

- **Method: Cox proportional hazards regression**

- **Endpoint: Progression or death**

MULTIVARIATE ANALYSIS II

■ *Variables considered:*

- Age
- ER status*
- Stage at Dx
- Type of initial surgery
- Adjuvant chemotherapy*
- Radiation therapy pretransplant
- Hormonal therapy pretransplant
- Anthracyclines pretransplant
- Interval from diagnosis to metastases

- Interval from metastases to transplant
- Sites of metastatic disease*
- Response to chemotherapy*
- Karnofsky Score pretransplant
- High-dose chemotherapy regimen
- Graft source
- Growth factors posttransplant
- Year of transplant

AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER FACTORS ASSOCIATED WITH PFS

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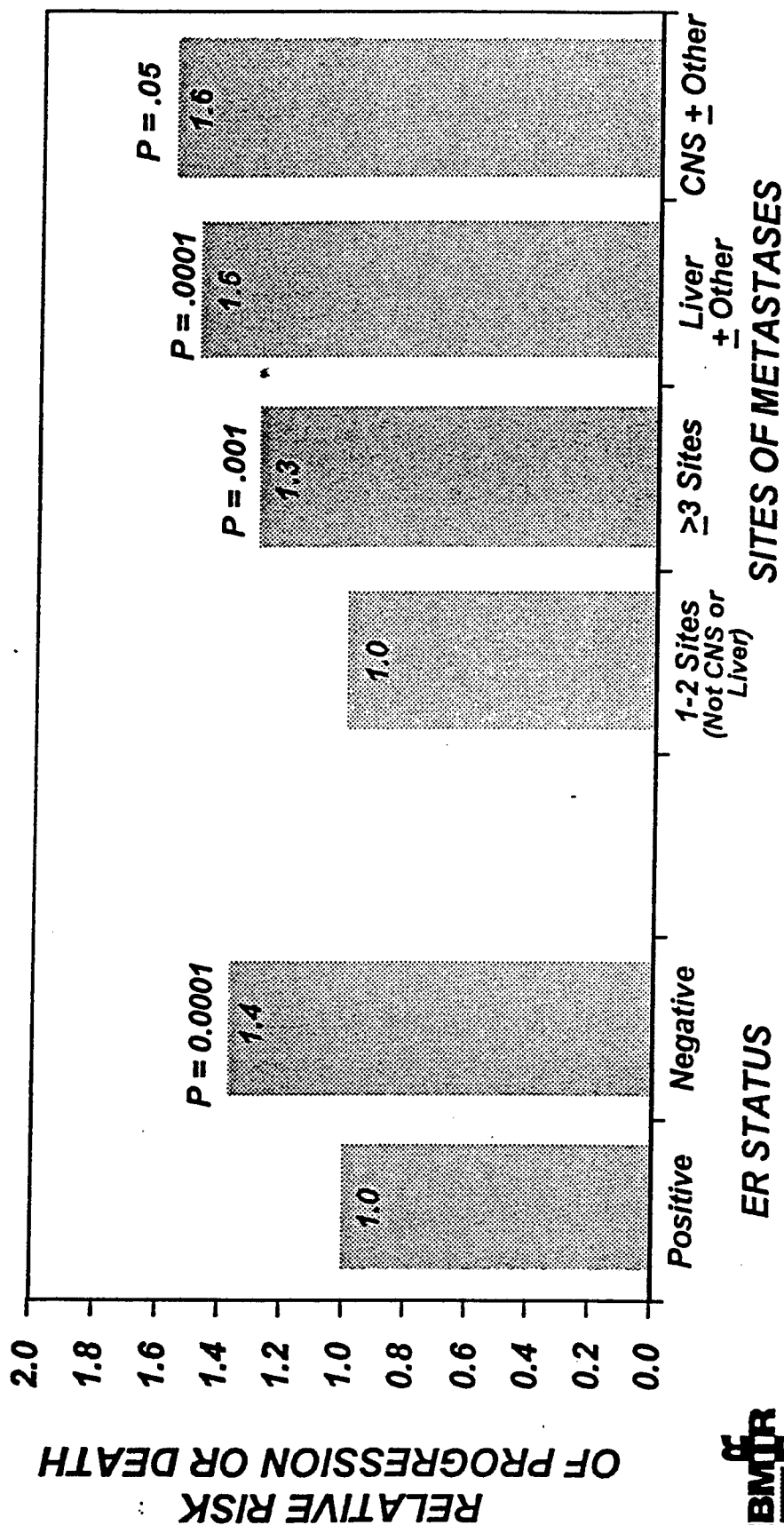
AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER FACTORS ASSOCIATED WITH PFS

PROBABILITY OF PROGRESSION-FREE SURVIVAL AFTER AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER BY ESTROGEN RECEPTOR STATUS
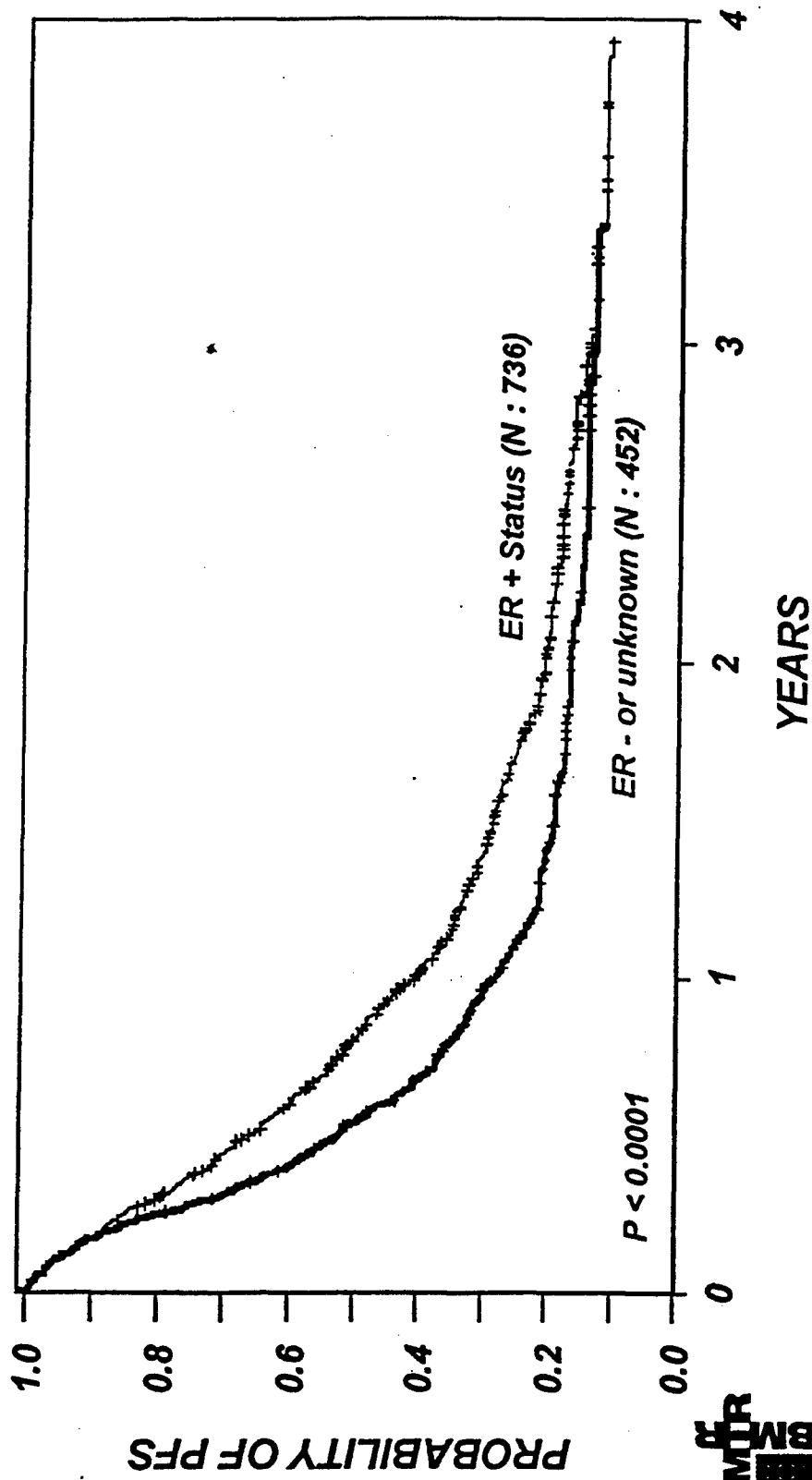
ER + Status (N : 736)

ER - or unknown (N : 452)

P < 0.0001

PROBABILITY OF PFS

YEARS

MBC97_9.wmf

PROBABILITY OF PROGRESSION-FREE SURVIVAL AFTER AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER BY SITES OF METASTATIC DISEASE PRETRANSPLANT
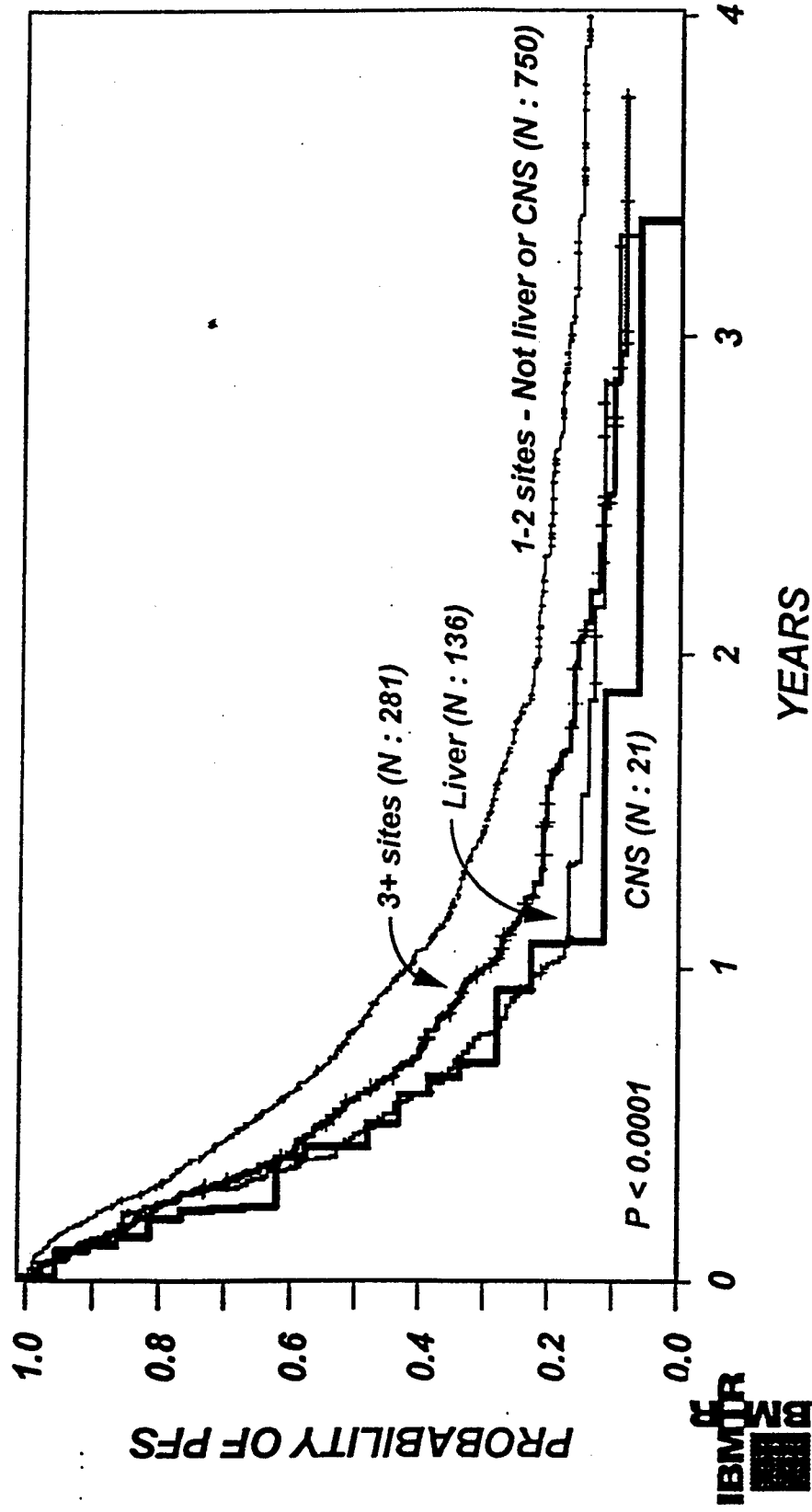
PROBABILITY OF PROGRESSION-FREE SURVIVAL AFTER AUTOTRANSPLANTS FOR METASTASTATIC BREAST CANCER BY ADJUVANT CHEMOTHERAPY
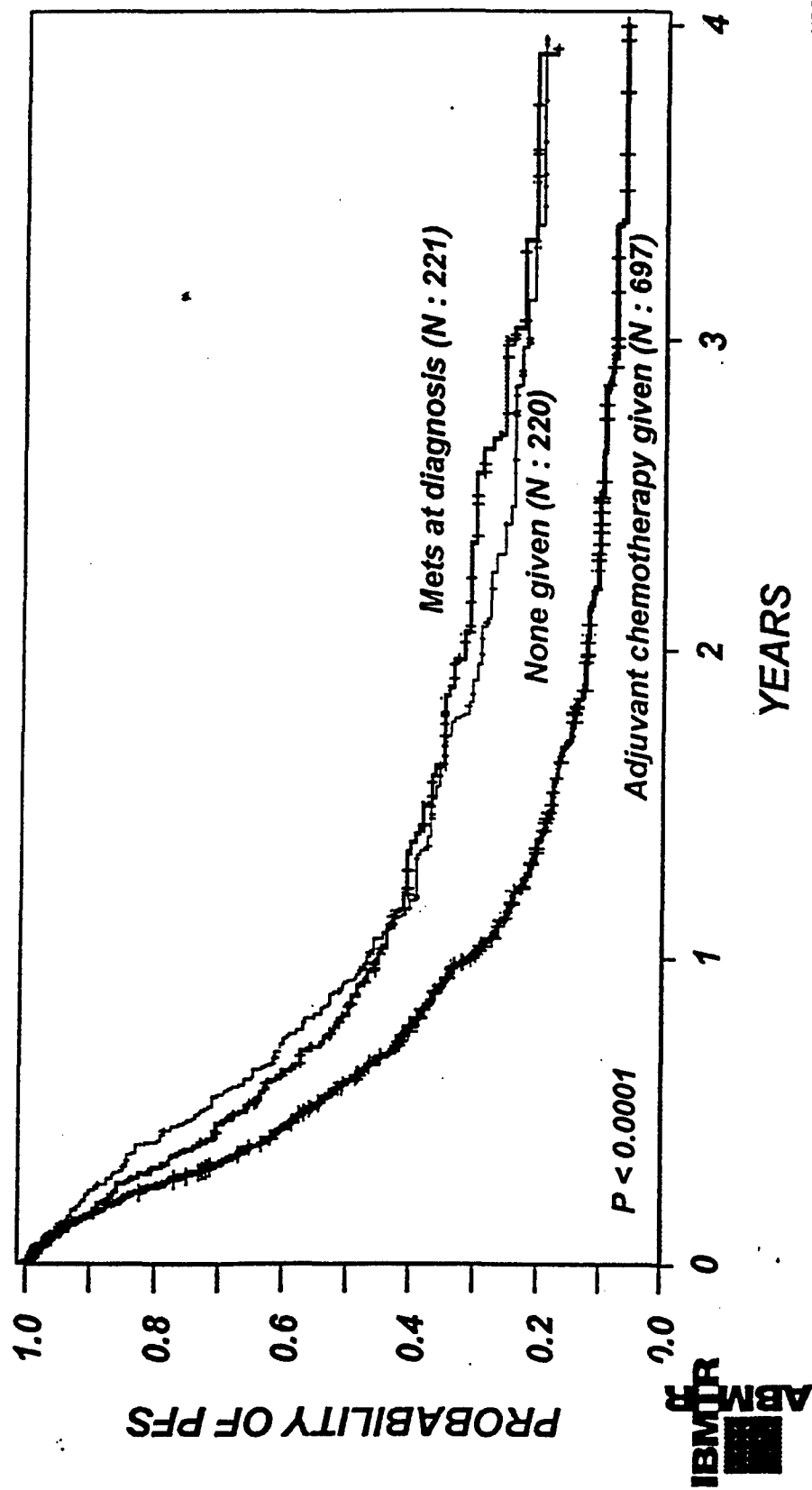
PROBABILITY OF PROGRESSION-FREE SURVIVAL AFTER AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER BY PRETRANSPLANT CHEMOTHERAPY SENSITIVITY

CR vs IND/UNK (P : 0.1)
CR vs PR (P < 0.0001)
PR vs RESISTANT (P : 0.02)

CR (N : 263)

IND/UNK (N : 169)

PR (N : 375)

RESISTANT (N : 330)

P < 0.0001

PROBABILITY OF PFS

YEARS

MBC97_10.wmf
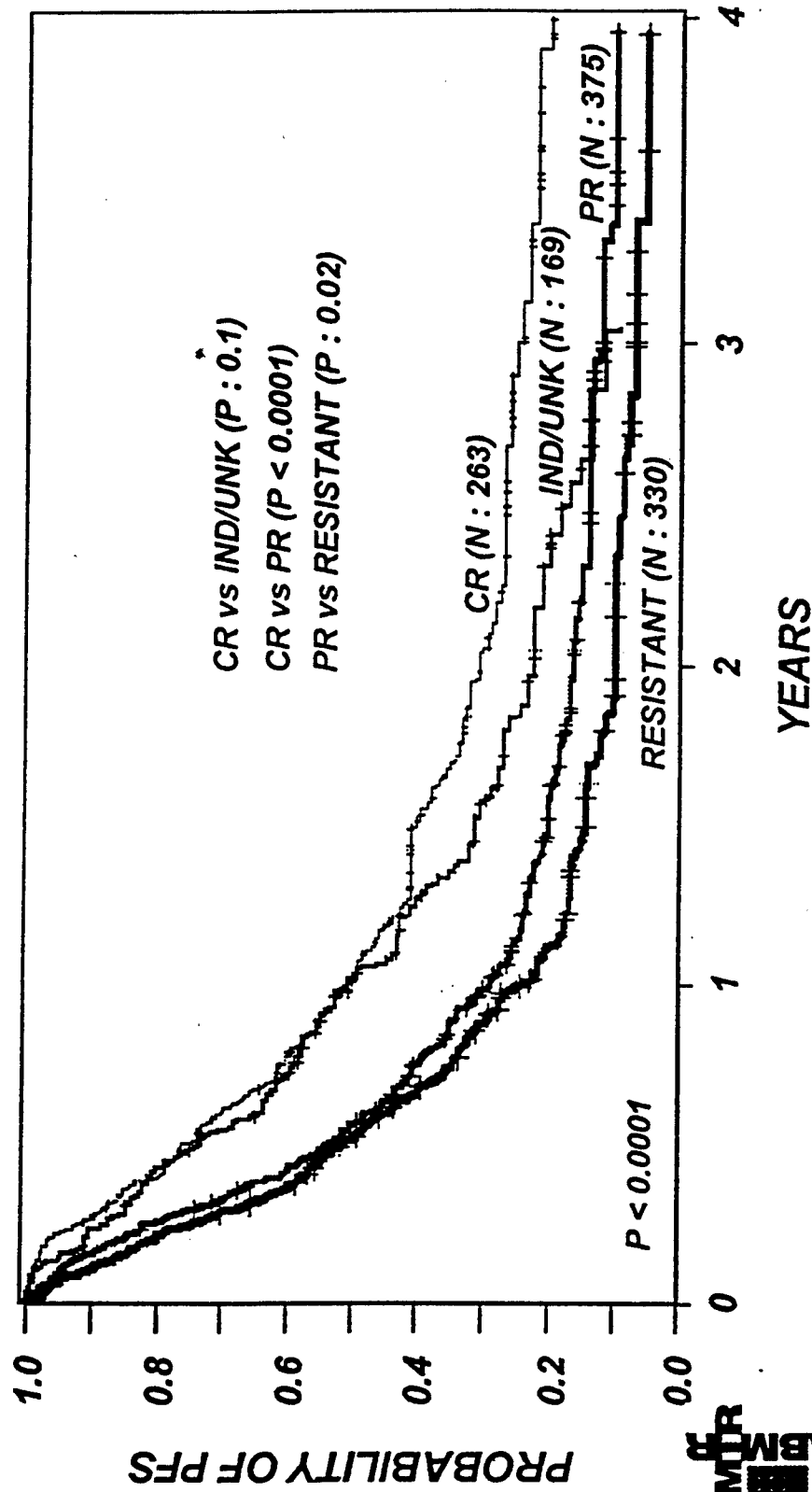
CONCLUSIONS

■ *Higher progression-free survival:*
- No prior adjuvant chemotherapy
- ER-positive disease
- No liver or CNS metastases
- Metastases limited to 1-2 sites
- CR prior to transplant

■ *No difference in progression-free survival among most commonly used high-dose chemotherapy regimens*

AUTOTRANSPLANTS FOR ACUTE HIGH RISK PRIMARY BREAST CANCER
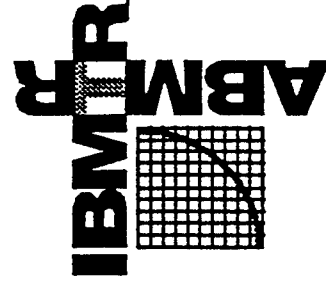
A Preliminary Analysis from

Autologous Blood and Marrow Transplant Registry-North America

IBMTR / ABMTR

PATIENTS

- 466 women receiving autotransplants for Stage II (n = 206), Stage III (n = 191) or inflammatory (n = 69) breast cancer

- Autotransplant done 1989-1995 in 52 centers reporting data to the ABMTR

AUTOTRANSPLANTS FOR HIGH-RISK PRIMARY BREAST CANCER

Patient Characteristics 1

N:	466	
Median age (range):	43 (24-66) y	
Performance Score <90:	5%	
ER status:	33%	Negative
	60%	Positive
	7%	Not tested/borderline
Number of axillary nodes:	20 (0-40)	
	4%	<9
	96%	>9
Size of primary tumor:	16%	<2 cm
	45%	2-4 cm
	39%	>4 cm

AUTOTRANSPLANTS FOR HIGH-RISK PRIMARY BREAST CANCER

Prior Treatment

Surgery pretransplant:
- 11% Lumpectomy
- 85% Mastectomy
- 4% None

Adjuvant chemotherapy:
- 65% CAF/FAC
- 27% Other adriamycim
- 8% Other

Radiation therapy pretransplant: 15%

Hormonal therapy pretransplant: 13%

Interval diagnosis to translant: 7 (3-18) m

AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER
Transplant Characteristics

Graft source:
- 46% BM
- 27% PBSC
- 27% BM & PBSC

Growth factors posttransplant: 93%

Radiation posttransplant: 60%

Hormone therapy posttransplant: 43%

Year of transplant:
- 5% 1989-90
- 35% 1991-92
- 61% 1992-95

AUTOTRANSPLANTS FOR HIGH-RISK PRIMARY BREAST CANCER

N = 466

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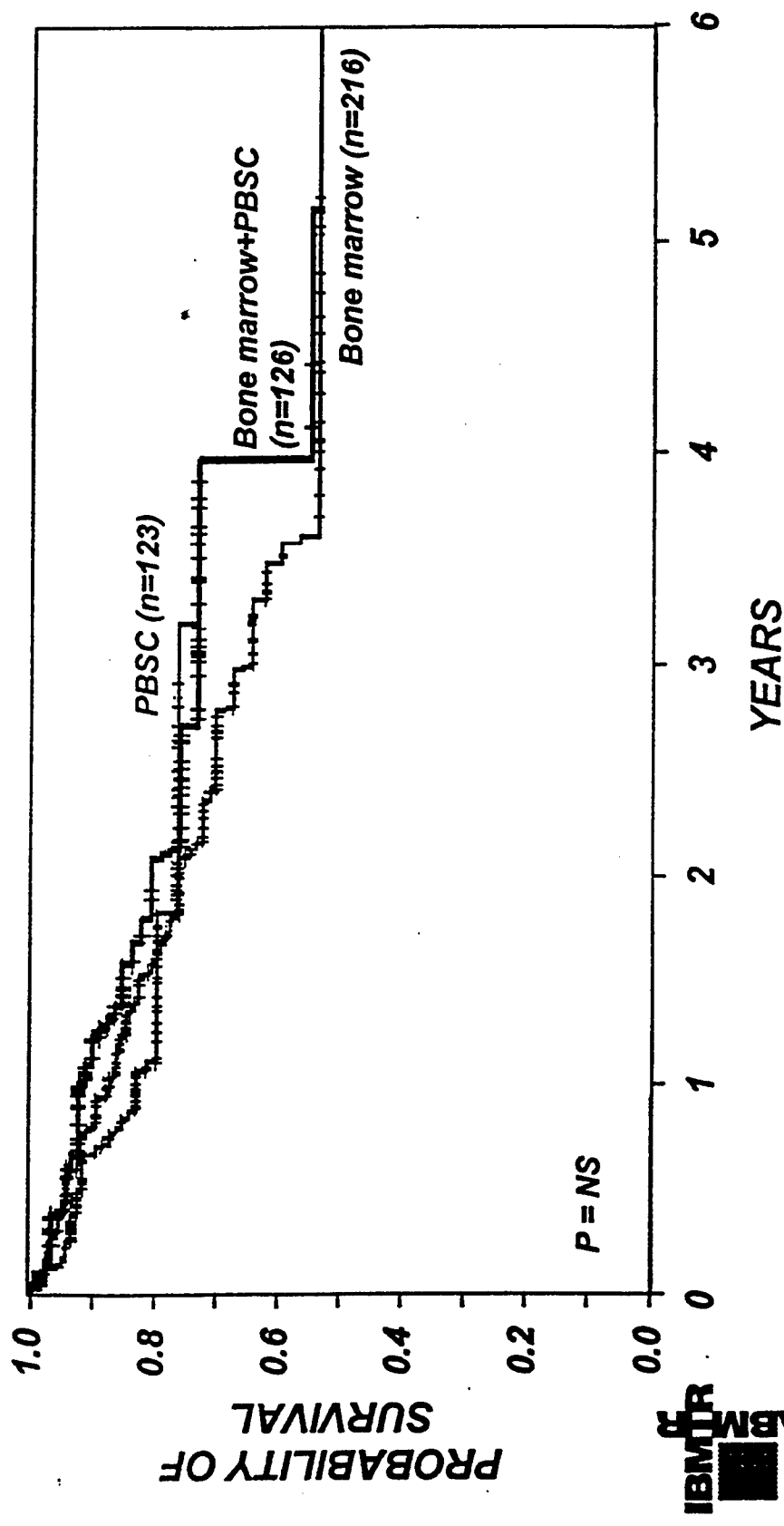
HIGH-DOSE
CHEMOTHERAPY

CBP

CT

Other

ICE

CTM

CTCb

IBMTR
ABMTR

PROBABILITY OF SURVIVAL
AFTER AUTOTRANSPLANT FOR
HIGH-RISK PRIMARY BREAST CANCER
1989-1995

Stage II (n=206)

Stage III (n=191)

Inflammatory (n=69)

Stage II vs Stage III, P = NS
Stage II vs Inflammatory, P = .001
Stage III vs Inflammatory, P = .0002

PROBABILITY OF SURVIVAL

YEARS

PBC97_3.wmf

IBMTR
ABMTR

PROBABILITY OF PFS
AFTER AUTOTRANSPLANT FOR
HIGH-RISK PRIMARY BREAST CANCER
1989-1995

Stage II (n=206)

Stage III (n=191)

Inflammatory (n=69)

Stage II vs Stage III, P = .9788
Stage II vs Inflammatory, P = .0006
Stage III vs Inflammatory, P = .0004

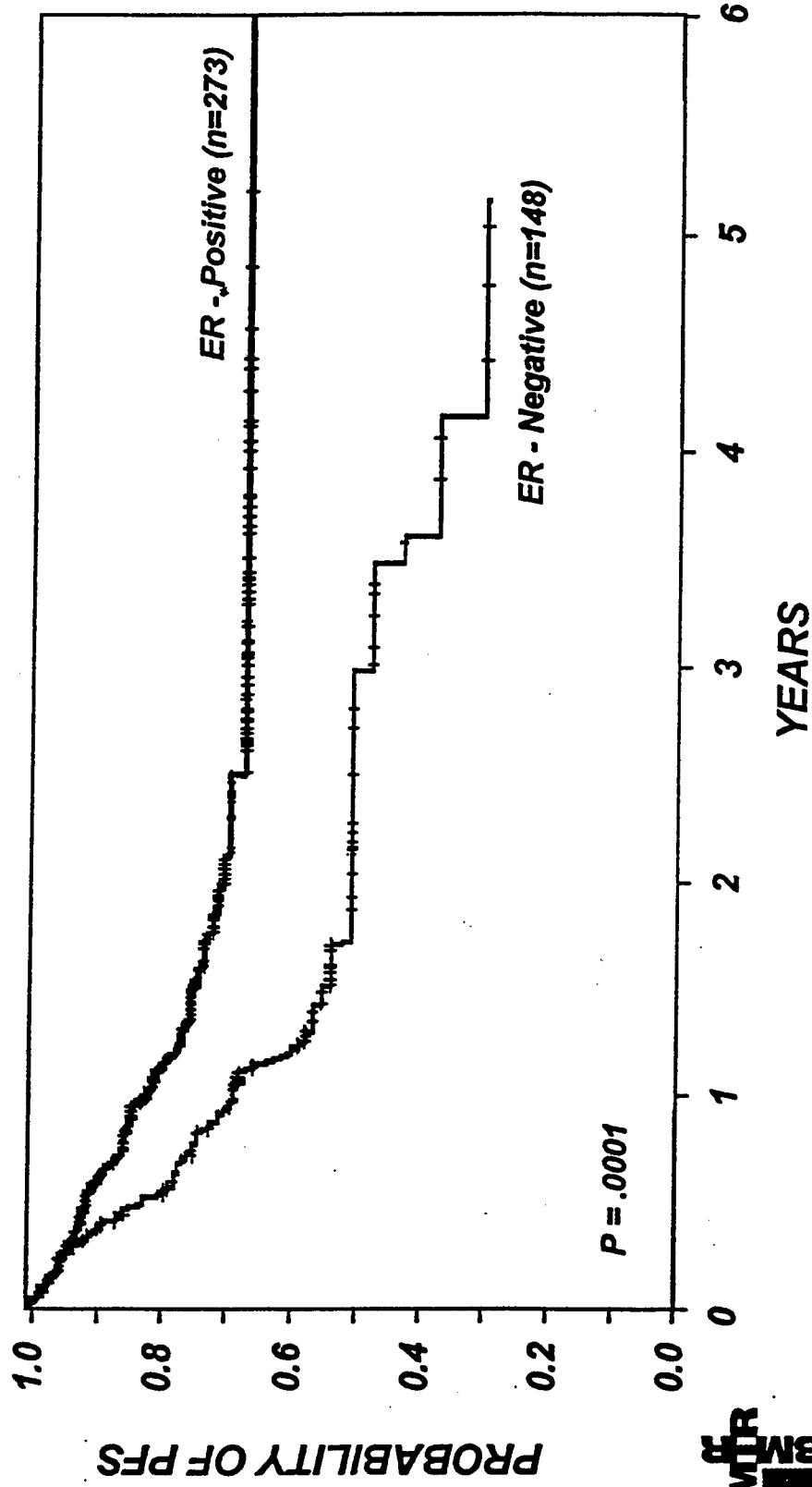YEARS

PROBABILITY OF PFS

PBC97_5.wmf

IBMTR / ABMTR

PROBABILITY OF SURVIVAL AFTER AUTOTRANSPLANT FOR HIGH-RISK PRIMARY BREAST CANCER, BY GRAFT TYPE

PROBABILITY OF PFS AFTER
AUTOTRANSPLANT FOR
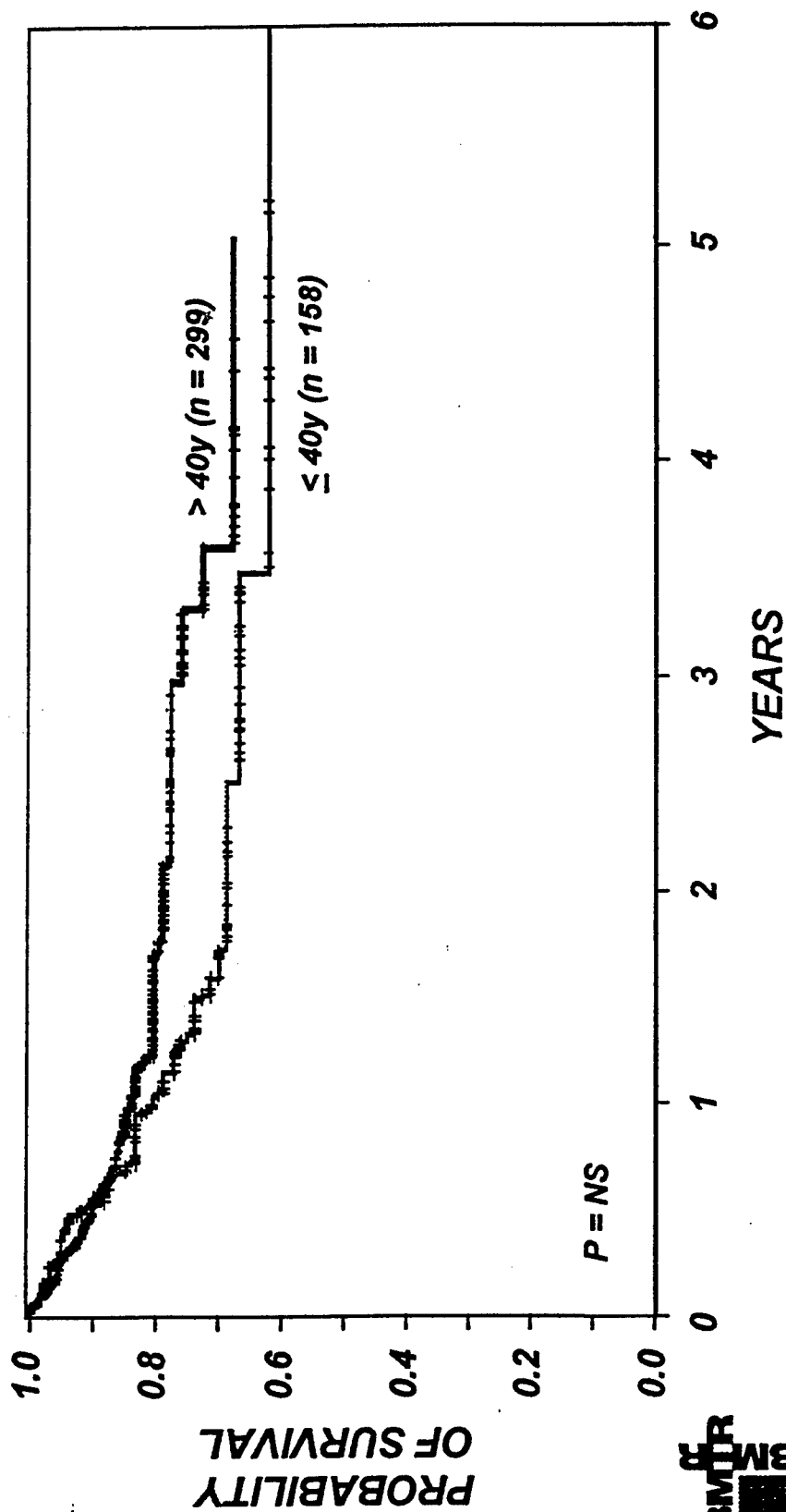HIGH-RISK PRIMARY BREAST CANCER
BY GRAFT TYPE

PROBABILITY OF SURVIVAL
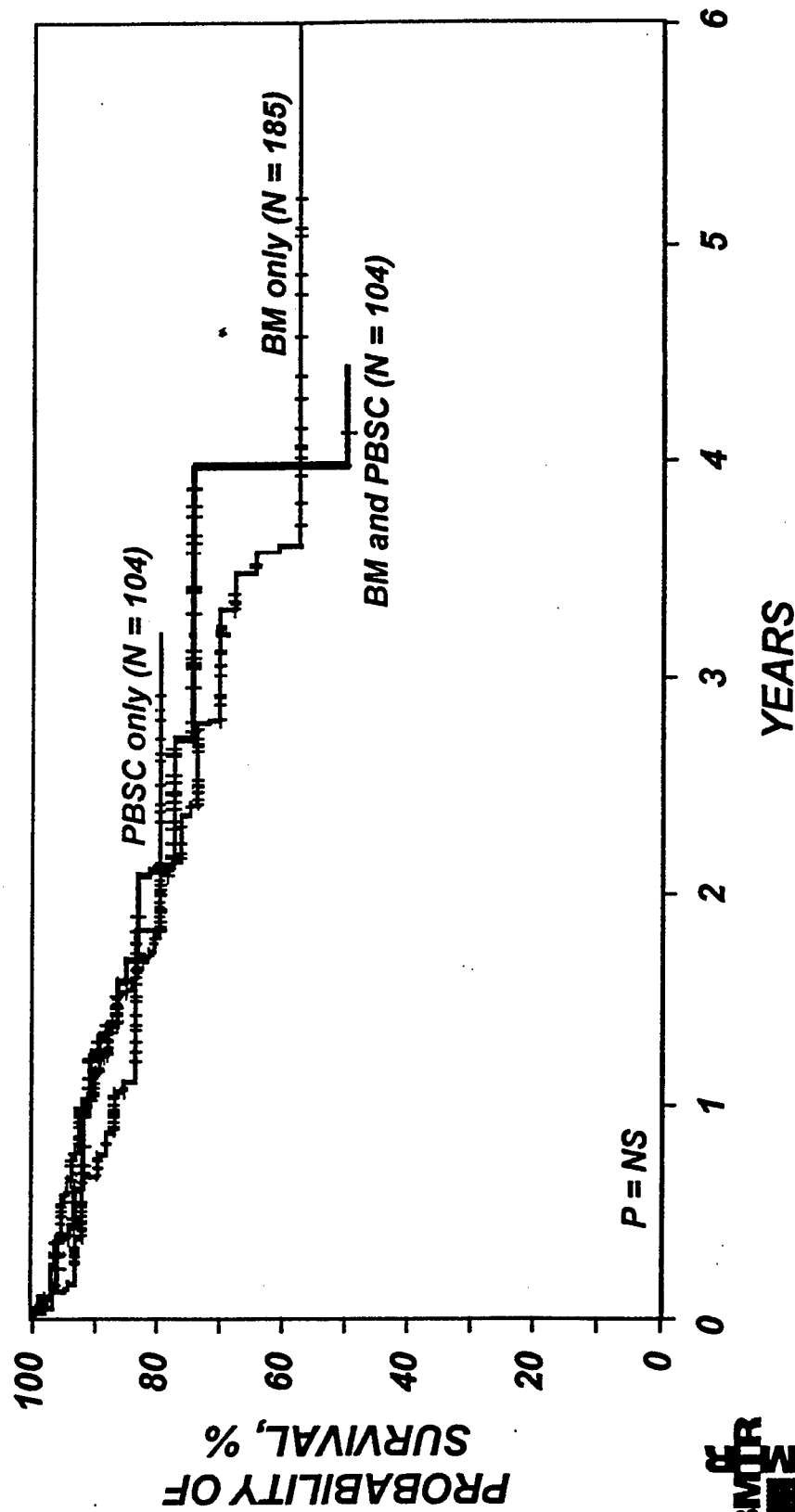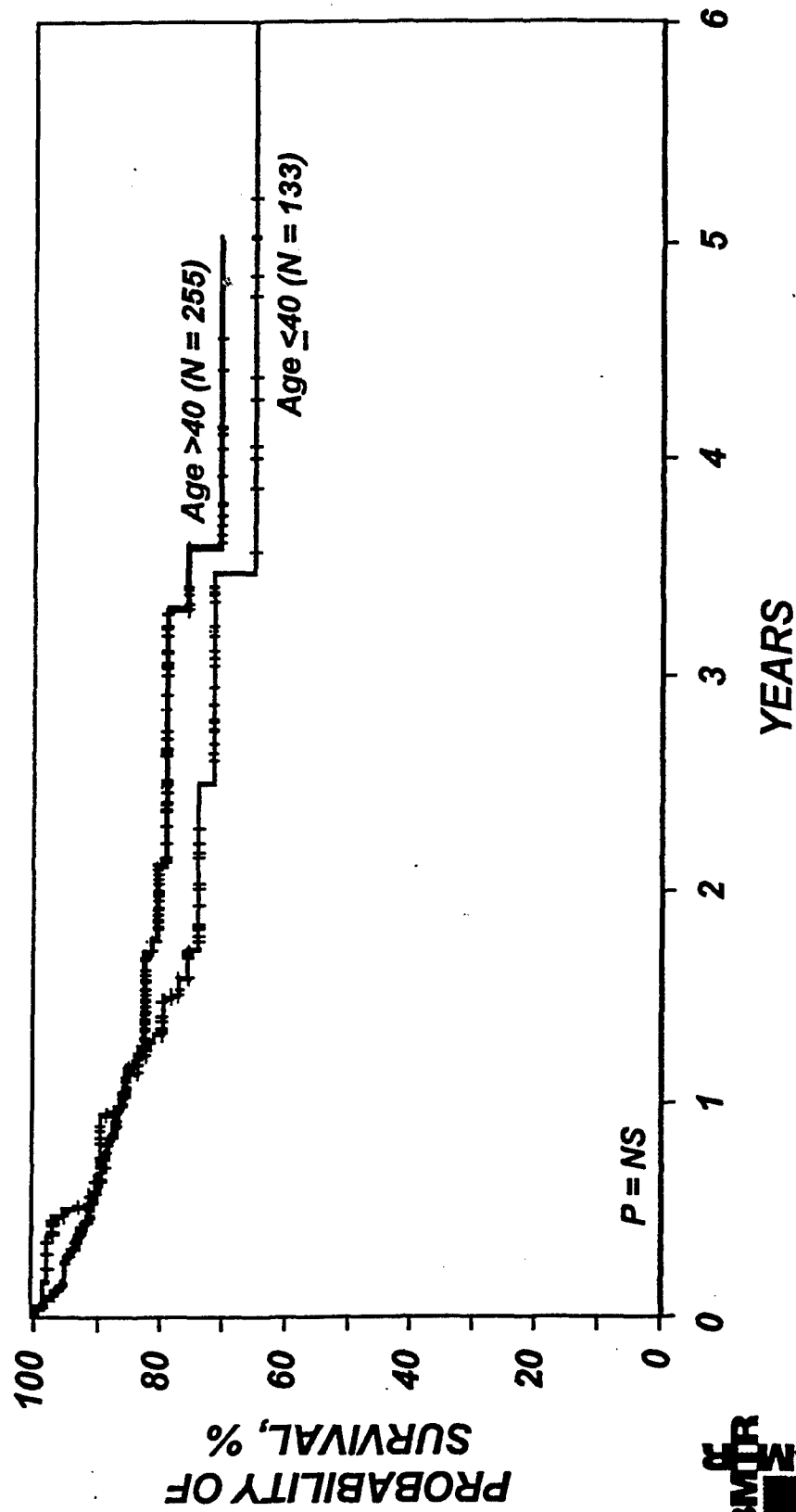AFTER AUTOTRANSPLANT FOR
HIGH-RISK PRIMARY BREAST CANCER,
1989-1995

PBC97_4.wmf

PROBABILITY OF PFS
AFTER AUTOTRANSPLANT FOR
HIGH-RISK PRIMARY BREAST CANCER
1989-1995

ER - Positive (n=273)

ER - Negative (n=148)

P = .0001

YEARS

PROBABILITY OF PFS

PBC97_7.wmf

ABMTR
IBMTR

PROBABILITY OF SURVIVAL AFTER AUTOTRANSPLANT FOR HIGH-RISK PRIMARY BREAST CANCER BY AGE AT TRANSPLANT

> 40y (n = 299)

≤ 40y (n = 158)

P = NS

PROBABILITY OF SURVIVAL

YEARS

PROBABILITY OF SURVIVAL AFTER
AUTOTRANSPLANTS FOR STAGE II / III BREAST CANCER
BY GRAFT TYPE, 1989-1995

P887_3.wmf

PROBABILITY OF SURVIVAL AFTER
AUTOTRANSPLANTS FOR STAGE II / III BREAST CANCER
BY AGE AT TRANSPLANT

P897_2.wmf

PROBABILITY OF SURVIVAL AFTER
AUTOTRANSPLANTS FOR STAGE II / III BREAST CANCER
BY ESTROGEN RECEPTOR STATUS, 1989-1995
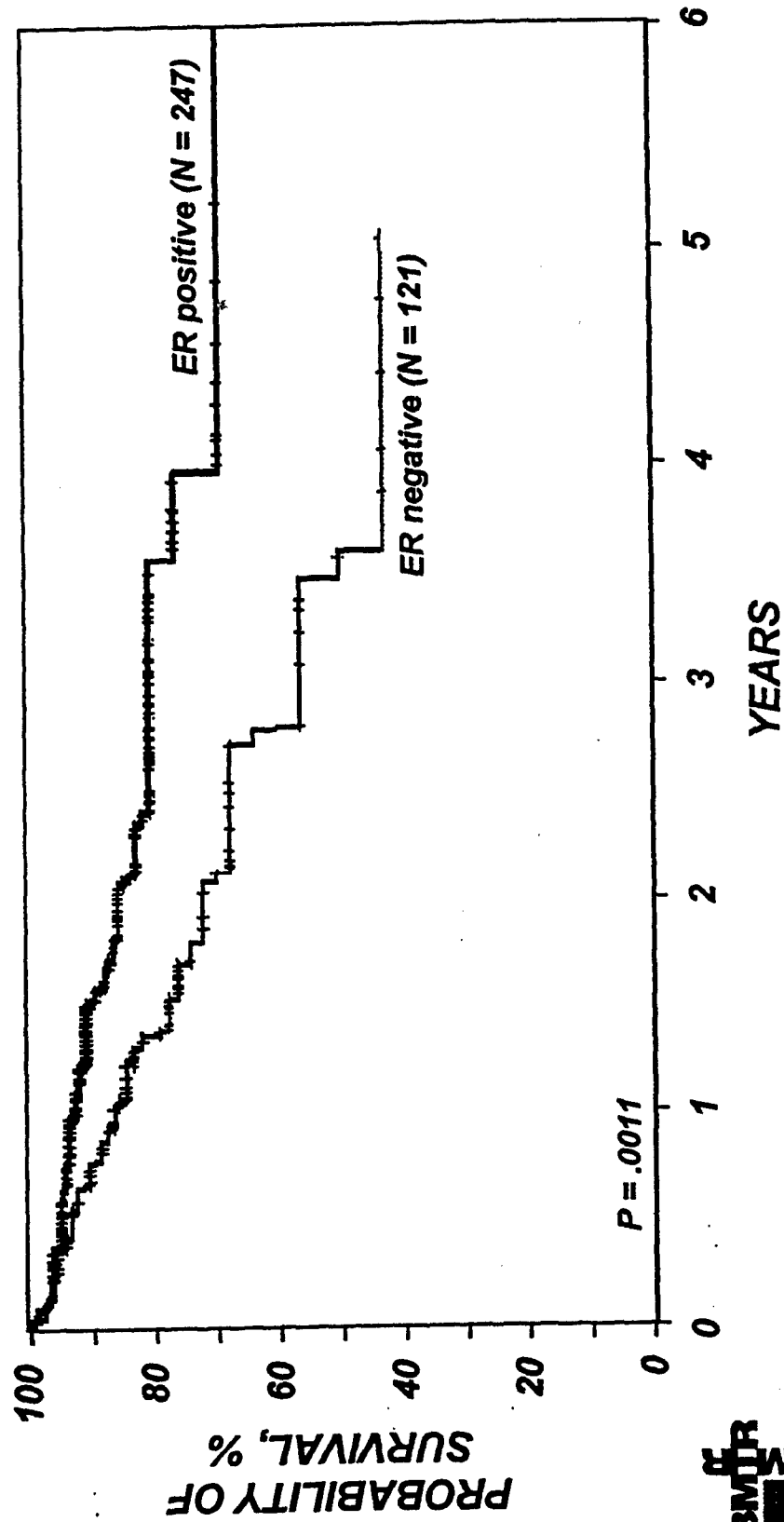
QUESTIONS

Does high-dose chemotherapy cure breast cancer?

Does high-dose chemotherapy prolong survival?

Can efficacy be improved by altering drugs, doses and/or schedules?

Are there late effects of high-dose chemotherapy?

AUTOTRANSPLANTS IN MEN WITH BREAST CANCER

A Report from

the Autologous Blood & Marrow Transplant Registry

IBMTR
ABMTR
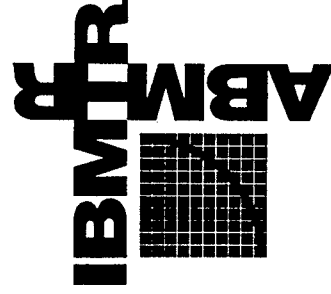
MALE BREAST CANCER

- <1% of all breast cancers

- Annual Incidence: <1 in 100,000 men

- More advanced stage at presentation

- Median Age: 5-10 yrs greater than women

- 80-90% estrogen and progesterone receptor positive

MALE BREAST CANCER
- Outcomes -

- Same as for women when matched for histopathology, receptor state and disease stage
  - □ Willsher et al. Ann J Surg, 1997
  - □ Cutuli et al. Eur J Cancer, 1995
  - □ Donegan & Redlich. Surg Clin N Amer, 1996
  - □ Borgen et al, Ann Surg Oncol, 1997

- Poorer outcome
  - □ Joshi et al. Cancer, 1996

MALE BREAST CANCER
- Therapy -

- ■ Surgery
- ■ Radiation
- ■ Chemotherapy
- ■ Hormone therapy
- ■ What is the role of autotransplant?

MALE BREAST CANCER
- Autotransplants -

- 13 of 3,254 autotransplants for breast cancer reported to the ABMTR

- January, 1989 to January, 1996

- Treated at 11 centers

- 10 autotransplants as adjuvant therapy

- 3 autotrasplants for Stage 4 disease

AUTOTRANSPLANTS IN MEN WITH BREAST CANCER
- Patient and Disease Characteristics (I) -

Number   13

Age, median (range)   50 (32-60) y

KPS pretransplant

  ≥90%   12 (92%)

  80%   1 (8%)

Stage

  II   6 (46%)

  III   3 (23%)

  III inflammatory   1 (8%)

  IV   3 (23%)

AUTOTRANSPLANTS IN MEN WITH BREAST CANCER
- Patient and Disease Characteristics (II) -

Estrogen receptor positive   12/12 (100%)   1 not tested

Progesterone receptor positive   11/12 (92%)   1 not tested

Number of positive axillary nodes, median (range)   14 (0-21)   6 Stage II pts $\geq$10+ nodes

Mastectomy pretransplant   12/13 (92%)

Interval from Dx → BMT, median (range)   6 (4-9) m   12, 31, 32m
    10 adj pts   3 met pts

Plm98_7.ppt

AUTOTRANSPLANTS IN MEN WITH BREAST CANCER
- Transplant Characteristics -

N   13

Graft source

Bone marrow   3 (23%)

PBSC   8 (62%)

Bone marrow + PBSC   2 (15%)

Conditioning regimen

Cyclophosphamide +

Thiotepa + Carboplatin   5 (38%)

Alkylator based regimen   8 (62%)

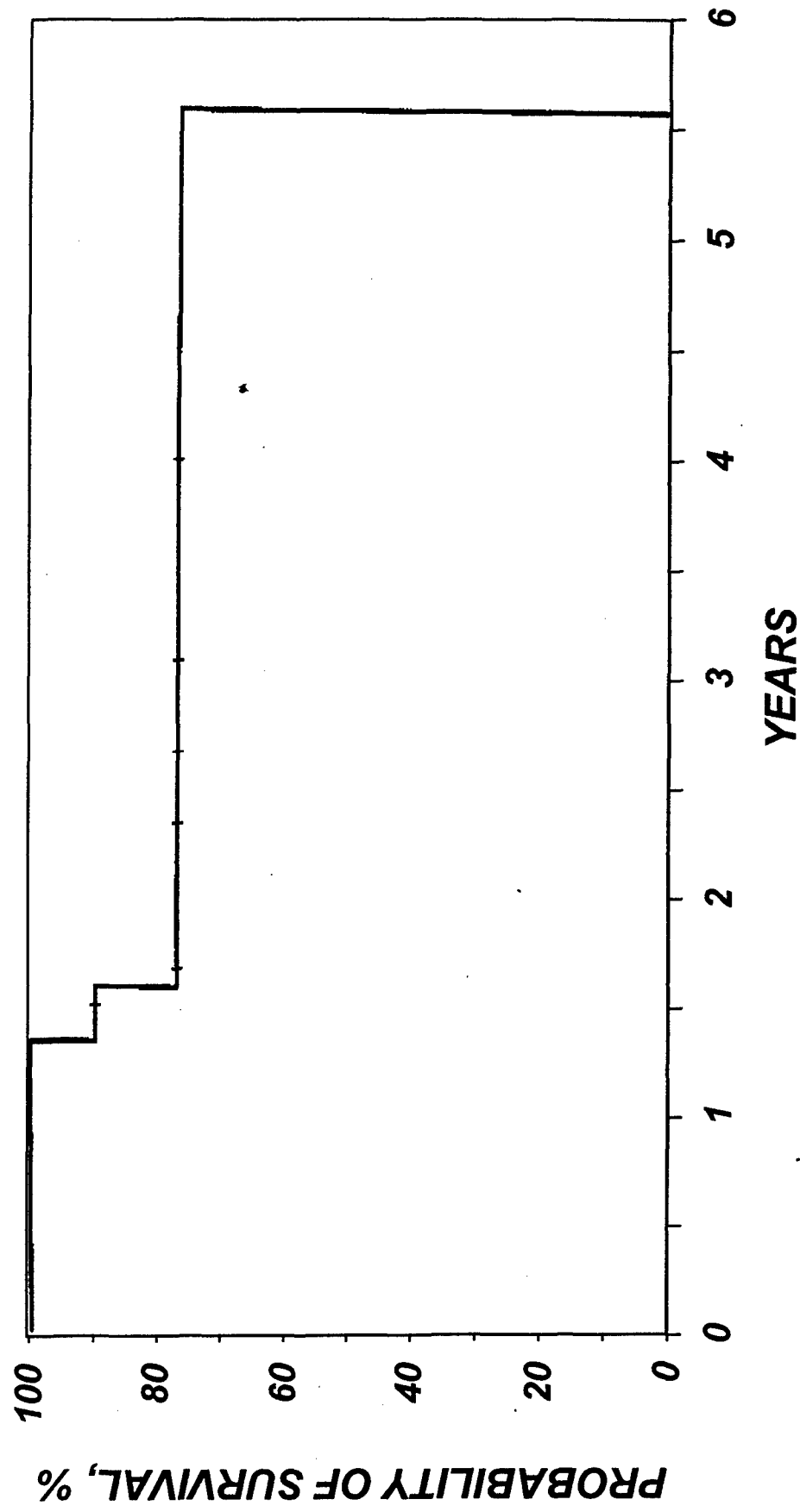# AUTOTRANSPLANTS IN MEN WITH BREAST CANCER
- Outcomes (I) -

|	
Time to ANC >1,000 cells / μl, median (range)	12 (8-22) d
Time to platelets >25,000 / μl, median (range)	14 (6-20) d
Non-myeloid grade 4 toxicity	0
Myelodysplastic syndrome	0
Primary chest wall radiation, adj pts	9
Hormonal therapy post BMT, adj pts	6

AUTOTRANSPLANTS IN MEN WITH BREAST CANCER
- Outcomes (II) -

	Disease-free Survival, median, range	Disease-free	Relapses, time after BMT	Death, time after BMT
Adjuvant patients	23 (6-50) m	7/10 (70%)	3, 5, 50m	16, 19, 67m
Metastatic patients	Not applicable	0/3 (0%)	5, 7, 16m 2 CR, 1 SD	12, 13m 1 alive @ 27m

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PROBABILITY OF SURVIVAL AFTER
AUTOLOGOUS TRANSPLANTS IN MALES WITH
HIGH-RISK PRIMARY BREAST CANCER

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PROBABILITY OF DFS AFTER
AUTOLOGOUS TRANSPLANTS IN MALES WITH
HIGH-RISK PRIMARY BREAST CANCER

BCM97_3.ppt
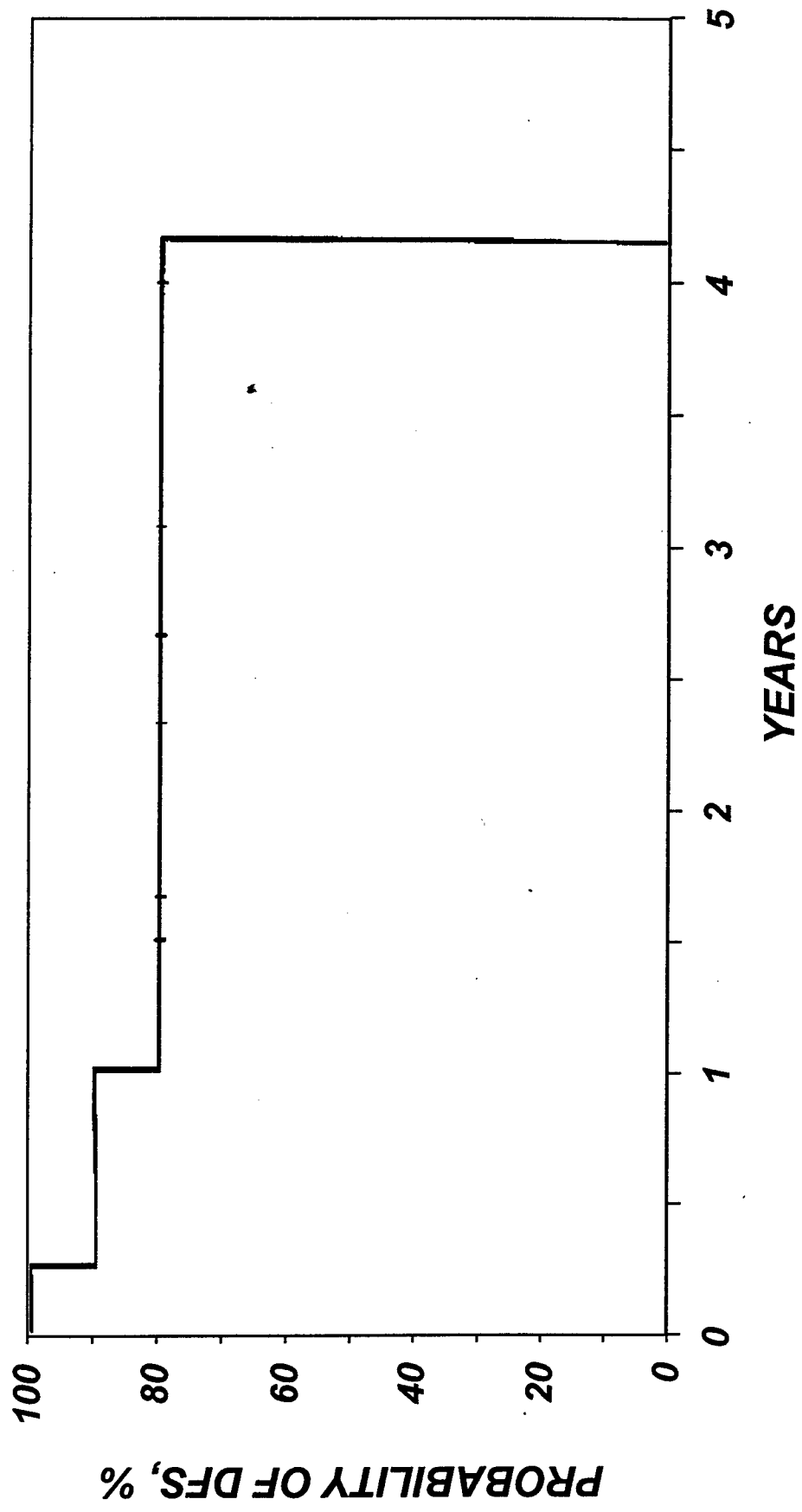
CONCLUSIONS (I)

- The outcome of men with breast cancer receiving autotransplants appears comparable to women treated with identical therapy for similar stage disease

- Patients treated with autotransplant for high risk, ≥ 10 node positive disease or Stage III disease appear to do well with this therapy

CONCLUSIONS (II)

- *Few metastatic disease patients' disease have been treated with autotransplant*

- *No patients developed non-myeloid grade 4 toxicity or myelodysplasia*

- *Most patients received additional therapy consisting of radiation or hormone treatment*

CONCLUSIONS (III)

- Indications for high-dose therapy that develop in trials in women should be applicable in men

- Reporting of cases to the ABMTR is encouraged

- Should male breast cancer patients be included in large randomized studies for women with breast cancer?

INVESTIGATORS

- DD Hurd, MD

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- SC Murphy, MS

- KS Antman, MD

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- J Doroshower, MD

- CO Freytes, MD

- RP Gale, MD, PhD

- LA Kalman, MD

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SOUTHFIELD, L.P
SPRING BRANCH, L.P.
VILLAGE, L.P.

December 16, 1998

Via Facsimile: 414/456-6530

Dr. Mary Horowitz
IBMTR/ABMTR
Medical College of Wisconsin
8701 Watertown Plank Rd.
Milwaukee, Wisconsin 53226

Dear Dr. Horowitz:

As you are aware, my wife Dede has recurrent breast cancer in the bone marrow. After Dede's recurrence of breast cancer, we met with the top high dose chemotherapy doctors in the country, as well as the top breast oncologist. We were always given anecdotal information, but there was no hard data from which an analytical decision could be made.

I offered to fund a program between three of the major hospitals to create a common database for high dose treatment of breast cancer. At first, all three hospitals agreed, but in the end, there was no follow-through or real commitment, and the proposal was not implemented.

The emphasis among the best doctors and hospitals is to develop a cure or better treatment than currently exist. Our problem has been to try to find the best available known treatment. There is a lack of hard data on outcome for breast cancer patients with specific characteristics of illness. Your national database for high dose chemotherapy has been the best source of information to evaluate the risk and benefits of high dose versus conventional dose therapy. Your information has been extremely beneficial to my wife in helping her make her decision for treatment.
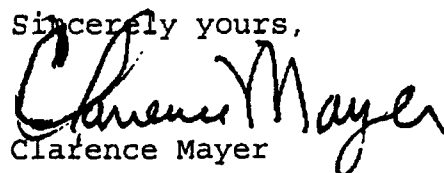
I believe that in all areas of treatment, a database should exist which allows patients and physicians access to data which shows outcome for patients who have certain characteristics of illness.

I believe your program sets the standard that should be available for treatment of all serious illness. We very much appreciate your help, guidance and support.

Sincerely yours,

Clarence Mayer

CM/jn

cc: Mrs. Dede Mayer
     Ms. Sylvia Mayer Baker
     Ms. Laura Mayer

:mayece\0225571:121698

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MCMR-RMI-S   (70-1y)   28 Jan 00

MEMORANDUM FOR Administrator, Defense Technical Information
         Center, ATTN: DTIC-OCA, 8725 John J. Kingman
         Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has
reexamined the need for the limitation assigned to technical
report written for Grant DAMD17-95-1-5002. Request the limited
distribution statement for Accession Document Number ADB247840 be
changed to "Approved for public release; distribution unlimited."
This report should be released to the National Technical
Information Service.

2. Point of contact for this request is Ms. Virginia Miller at
DSN 343-7327 or by email at virginia.miller@det.amedd.army.mil.

FOR THE COMMANDER:

                              PHYLIS M. RINEHART
                              Deputy Chief of Staff for
                              Information Management